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CONTENTS

...OF PLASMA CELL DYSCRASIAS

	Comments and Examples
	Especially carcinomas of the prostate, kidney, GI tract, breast, and biliary tree
	Chronic cholecystitis, osteomyelitis, TB, pyelonephritis, RA
	Lichen myxedematosus, liver disease, thyrotoxicosis, pernicious anemia, myasthenia gravis, Gaucher's disease, familial hypercholesterolemia, Kaposi's sarcoma
	Occurs in apparently healthy persons; age-related incidence
IgM	
IgG, IgA, light chains (Bence Jones) only, IgD, IgE, nonsecretory	
Usually light chains (Bence Jones) only, but occasionally intact immunoglobulin molecules (IgG, IgA, IgM, IgD)	
IgG heavy chain (γ-chain) disease	
IgA heavy chain (α-chain) disease	
IgM heavy chain (μ-chain) disease	
IgD heavy chain (δ-chain) disease	
Associated with drug hypersensitivity, viral infections, and heart surgery	

...or other lymphoproliferative

...nemia is clinically distinct ...and other plasma cell dyscra... ...es a lymphomatous disease. ...known. Men are affected ... women; the median age is ...

..., manifestations of macro... ...due to the large amount of ...eight macroglobulin circu... ...Some of these monoclonal ... antibodies directed to au... ...umatoid factors) or to I an... ...tinins).

Symptoms and Signs

Most patients are asymptomatic, but many present with manifestations of the **hyperviscosity syndrome:** fatigue, weakness, skin and mucosal bleeding, visual disturbances, headache, and other changing neurologic manifestations. When predominant, cardiopulmonary abnormalities are due to circulatory impairment caused by an increased plasma volume. Cold sensitivity or Raynaud's phenomenon may be due to a cryoglobulin or cold agglutinin. Recurrent bacterial infections are a major problem in some patients.

Examination may disclose generalized lymphadenopathy, purpura, hepatosplenomegaly, and marked engorgement and localized narrowing of retinal veins, which resemble sausage links. Amyloidosis occurs in 5% of patients.

Diagnosis

Most diagnoses of monoclonal gammopathy are preceded by incidental discovery of elevated serum total protein or anemia. The diagnosis is established by demonstrating a typical M spike on serum protein electrophoresis that proves to be IgM by immunoelectrophoresis or immunofixation.

Moderate anemia, marked rouleaux formation, and a very high ESR are typical. Leukopenia, relative lymphocytosis, and thrombocytopenia occasionally occur. Cryoglobulins, rheumatoid factor, or cold agglutinins may be present; if the latter are present, the direct Coombs' test usually is positive. Various coagulation and platelet function abnormalities may occur. Results of routine blood studies may be spurious if a cryoprotein is present or if viscosity is markedly increased. Normal immunoglobulins are decreased in 1/2 of patients.

Immunoelectrophoretic studies of concentrated urine frequently show a monoclonal light chain (usually κ), but gross Bence Jones proteinuria is unusual. X-rays of bones may show osteoporosis, but lytic lesions are rare. Bone marrow studies show a variable increase in plasma cells, lymphocytes, and plasmacytoid lymphocytes. PAS-positive material may be present in lymphoid cells, and the number of mast cells may be increased. In addition, lymph node biopsy is frequently interpreted as diffuse well-differentiated or plasmacytic lymphocytic lymphoma.

The hyperviscosity syndrome can be diagnosed by the funduscopic finding of retinal veins that resemble sausage links. Retinal hemorrhages, exudates, microaneurysms, and papilledema indicate late stages. Relative serum viscosity is usually > 4.0 (normal, 1.4 to 1.8) in patients with the hyperviscosity syndrome.

Prognosis and Treatment

The course is variable, but macroglobulinemia tends to be more benign than is myeloma. The median survival is about 5 to 7 yr. Age > 60 yr, anemia, and cryoglobulinemia are associated with shorter survival.

Often, patients require no treatment for many years. If hyperviscosity is present, initial management consists of plasmapheresis, which rapidly reverses bleeding and neurologic abnormalities caused by high IgM levels. Plasmapheresis often needs to be repeated.

Long-term treatment with oral alkylating drugs, usually chlorambucil, may be necessary in some patients; however, bone marrow toxicity (see below under MULTIPLE MYELOMA) can occur. Chlorambucil 0.03 to 0.09 mg/kg/day or pulses of 0.25 mg/kg/day for 4 days q 4 to 6 wk may be used. Melphalan or cyclophosphamide, as given for multiple myeloma, are possible alternatives, and oral prednisone (1 mg/kg/day for 4 days q 4 to 6 wk) may be added. Recent results with the purine analogs fludarabine and 2-chlorodeoxyadenosine have been encouraging and offer alternatives to patients unresponsive to standard oral alkylating drugs. Interferon reduces M protein in some patients.

MULTIPLE MYELOMA

(Plasma Cell Myeloma; Myelomatosis)

A progressive neoplastic disease characterized by marrow plasmacytomas (plasma cell tumors) and overproduction of an intact monoclonal immunoglobulin (IgG, IgA, IgD, or IgE) or Bence Jones protein (free monoclonal κ or λ light chains).

Multiple myeloma is often associated with multiple osteolytic lesions, hypercalcemia, anemia, renal damage, and increased susceptibility to bacterial infections; production of normal immunoglobulin is impaired. The incidence is estimated at 2 to 3/100,000 persons, the male:female ratio is 1.6:1, and most

patients are > 40 yr. The prevalence in blacks is twice that in whites.

Etiology and Pathogenesis

The etiology is unknown. A relationship is suggested by finding Kaposi's sarcoma–associated herpes virus in the dendritic cells cultured from myeloma patients. This virus encodes an interleukin-6 homologue; human interleukin-6 promotes myeloma growth and stimulates resorption of bone.

The specific cell of origin is unknown. Analysis of immunoglobulin gene sequences and cell surface markers suggests malignant transformation of a post–germinal center cell.

Pathology

Diffuse osteoporosis or discrete osteolytic lesions develop, usually in the pelvis, spine, ribs, and skull. Lesions are due to bone replacement by expanding plasmacytomas or a factor secreted by malignant plasma cells (osteoclast-activating factor). The osteolytic lesions are usually multiple but occasionally are solitary intramedullary masses. Extraosseous plasmacytomas are unusual but may occur in any organ, especially the upper respiratory tract.

Plasmacytomas produce IgG in about 55% of myeloma patients and IgA in about 20%; of these IgG and IgA patients, 40% also have Bence Jones proteinuria. Light chain myeloma is found in 15 to 20% of patients; their plasma cells secrete only free monoclonal light chains (κ or λ Bence Jones protein), and an M spike is usually absent on serum electrophoresis. Patients with the light chain subgroup tend to have a higher incidence of lytic bone lesions, hypercalcemia, renal failure, and amyloidosis than do other myeloma patients. IgD myeloma accounts for about 1% of cases; serum levels are often relatively low, and marked Bence Jones proteinuria (80 to 90% type λ) is characteristic. Only a few cases of IgE myeloma have been reported. Nonsecretory myeloma (no identifiable M component in serum or urine) is very rare (< 1% of cases).

Amyloid deposits (see Ch. 18) occur in 10% of myeloma patients and are especially likely in those with Bence Jones proteinuria.

Symptoms and Signs

Persistent unexplained skeletal pain (especially in the back or thorax), renal failure, or recurrent bacterial infections are the most common presentations. Pathologic fractures and vertebral collapse are common; the latter may lead to spinal cord compression and paraplegia. Renal failure (myeloma kidney) may be caused by extensive cast formation in the renal tubules, atrophy of tubular epithelial cells, and interstitial fibrosis. Anemia, sometimes with weakness and fatigue, predominates in some patients, and a few have manifestations of the hyperviscosity syndrome (see under MACROGLOBULINEMIA, above). Lymphadenopathy and hepatosplenomegaly are unusual.

Diagnosis

In the patient with a serum M protein, any one of three additional findings fulfills criteria for the diagnosis of myeloma: sheets or clusters of marrow plasma cells, osteolytic lesions (without evidence of metastatic carcinoma or granulomatous disease), or Bence Jones proteinuria > 300 mg/24 h.

Blood tests show a normocytic normochromic anemia with rouleaux formation. The WBC and platelet counts usually are normal. The ESR is often markedly elevated, sometimes > 100 mm/h, and BUN, serum creatinine, and serum uric acid are frequently elevated. A low anion gap is sometimes present. Hypercalcemia is found at diagnosis in about 10% of patients. The serum level of β_2-microglobulin is frequently elevated and correlates with myeloma cell mass.

Proteinuria is common because of excess synthesis and secretion of free monoclonal light chains. Chemical paper strip tests of urine do not reliably detect Bence Jones protein, and the heat test is often misleading, but sulfosalicylic acid and toluene sulfonic acid are useful screening tests. Significant albuminuria is rare in myeloma; its presence suggests coexisting amyloidosis or light chain deposition disease.

Serum protein electrophoresis shows a tall, narrow, homogeneous M spike in about 80% of patients; the mobility of the M spike may lie anywhere from the α_2 to the slow γ region. The remaining 20% of patients synthesize only free monoclonal light chains (Bence Jones protein), and their serum electrophoretic patterns display hypogammaglobulinemia without an M spike. However, in essentially all patients with light chain myeloma, a homogeneous M spike is demon-

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