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Hypergammaglobulinemia (Polyclonal Gammopathy)

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Continuing Education Activity

Hypergammaglobulinemia (polyclonal gammopathy)' refers to the overproduction of more than one class of immunoglobulins by plasma cells. It is most commonly associated with liver disease, acute or chronic inflammation, autoimmune disorders, and some malignancies. Hypergammaglobulinemia (polyclonal gammopathy) is generally considered a benign condition that does not progress to overt malignancy, contrary to monoclonal gammopathy of undetermined significance (MGUS). This activity outlines the evaluation and management of 'hypergammaglobulinemia (polyclonal gammopathy)' and highlights the role of the inter-professional team in evaluating and treating patients with this condition.

Objectives:

- Explain the pathophysiology of hypergammaglobulinemia (polyclonal gammopathy).
- Review the appropriate steps in evaluating a patient suspected of having hypergammaglobulinemia (polyclonal gammopathy).
- Identify the management considerations for patients with hypergammaglobulinemia (polyclonal gammopathy).
- Outline interprofessional team strategies for enhancing care coordination and communication to advance the evaluation and management of hypergammaglobulinemia (polyclonal gammopathy) and improve outcomes.

Access free multiple choice questions on this topic.

Introduction

Hypergammaglobulinemia (polyclonal gammopathy) refers to the overproduction of more than one class of immunoglobulins by plasma cells. It is most commonly associated with liver disease, acute or chronic inflammation, autoimmune disorders, and some malignancies.[1]

Hypergammaglobulinemia (polyclonal gammopathy) is generally considered a benign condition that does not progress to overt malignancy, contrary to monoclonal gammopathy of undetermined significance (MGUS).

Etiology

The exact etiology of hypergammaglobulinemia (polyclonal gammopathy) is unknown. However, the association between hypergammaglobulinemia (polyclonal gammopathy) and a heterogeneous group of conditions is well established. Among them, liver disease is the most common cause.[2]

Other important causes are autoimmune conditions such as Sjögren syndrome, hematologic disorders such as idiopathic neutropenia, nonhematologic malignancies, infections such as human immunodeficiency virus, IgG4-related disease (IgG4-RD), and iatrogenic (intravenous immunoglobulin therapy).[3][4]

Epidemiology

Hypergammaglobulinemia (polyclonal gammopathy) is relatively uncommon. The most extensive study on hypergammaglobulinemia (polyclonal gammopathy) shows that it predominately occurs in the older population with a median age of 58 years and an almost equal male-to-female ratio.[2] Some studies indicate a high prevalence in African American and black populations.[5]

Pathophysiology

Polyclonal B cell activation in various disease processes results in hypergammaglobulinemia (polyclonal gammopathy). However, the exact immunological cascade triggering polyclonal B-cell activation is not fully understood. Chronic antigenic stimulation, T cell-mediated B cell activation, cytokines (e.g., interleukin 6, 10), and defects in reticuloendothelial cells all play an essential role in immune responses. Also, genetic predisposition plays a vital role in immune response in various populations.[5]

The inflammatory cytokine IL-6 (Interleukin 6) plays an essential role in the pathogenesis of polyclonal gammopathy.[6][7] During an active infection, monocyte and macrophage recognize PAMPs (pathogen-associated molecular patterns) from microbes. Similarly, macrophages and monocyte recognize DAMP (Danger-associated molecular pattern) via TLR (toll-like receptor) during cellular damage. This recognition initiates a cascade of immune reactions, which ultimately induces the release of IL-6.[4]

For example, in multicentric Castleman disease, a large amount of IL-6 is expressed in the lymph node. Successful treatment of a patient with ‘Multicentric Castleman disease’ with IL-6 inhibitors such as siltuximab or tocilizumab proves the role of IL-6 in the disease process.[8][9][10][11]

IL-6 also plays an integral role in stimulating hepatocytes to produce various acute phase reactants (e.g., CRP, serum amyloid A, fibrinogen, hepcidin, and haptoglobin).[12]

IL-6 also activates naive CD4+ T cells to become helper T cells. Later, helper T-cell plays the leading role in B cell proliferation, B cell class switching, and maturation of B cells into immunoglobulin-secreting plasma cells. Furthermore, IL-6 supports chronic inflammation and autoimmunity by increasing Th17 (T helper 17) cells and decreasing regulatory T cells.

Although IL-6 is pivotal in the pathophysiology of polyclonal gammopathy in inflammatory conditions, polyclonal gammopathy can also occur without a significant inflammatory process.

In hepatic cirrhosis, damage to the Kupffer cell leads to inadequate immune surveillance of the liver.[4] This loss of hepatic immune surveillance and hemodynamic shunting from the portal circulation to the systemic circulation allows widespread immune response from enteric endotoxin and antigen. These lead to an increase in IgA and IgG production.[13]

In pulmonary sarcoidosis, local immunoglobulin production is related to activated T lymphocytes.[14]

Direct activation of B cells by various bacterial and viral proteins (e.g., HIV viral protein, HIV accessory protein Tat) is also noted in the pathophysiology of polyclonal gammopathy.[15]

History and Physical

Hypergammaglobulinemia (polyclonal gammopathy) itself does not cause any symptoms. In a patient with hypergammaglobulinemia (polyclonal gammopathy), most symptoms are related to the primary disorder causing

hypergammaglobulinemia (polyclonal gammopathy). Following the history and physical examination should be considered in a patient with hypergammaglobulinemia (polyclonal gammopathy):

- Signs of chronic liver disease
- Fever or any sign of infection
- Travel and exposures history
- Lymphadenopathy
- Skin lesions
- Arthritis
- Swelling of lacrimal, salivary, and parotid glands
- Hepatosplenomegaly
- Symptoms and signs of hyperviscosity syndrome
- Intravenous immunoglobulin therapy
- Family history of immunodeficiency[4]

Evaluation

'Hypergammaglobulinemia (polyclonal gammopathy)' is associated with a broad-based peak or band in the gamma region on Serum protein electrophoresis.[16]

When hypergammaglobulinemia (polyclonal gammopathy) is identified on serum protein electrophoresis, no further investigation is usually recommended in whom the cause is immediately evident in the clinical context.

However, the following diagnostic studies can be done to identify the underlying disorder.[4]

- Complete blood count and peripheral blood film
- ESR and C-reactive protein
- Liver enzymes (i.e., AST, ALT, ALP, and GGT)
- ANA, ANCA, complement C3, complement C4, and DAT
- Hepatitis B virus, hepatitis C virus, Epstein-Barr virus, human herpesvirus-8 serologies, and HIV serologies
- Imaging for liver disease, lymphadenopathy, and malignancy
- Bone marrow biopsy if lymphoma or hematological disorder suspected
- SPEP, UPEP, and quantitative immunoglobulin
- Quantitative immunoglobulins (i.e., IgM, IgG, IgA)
- lgG subclasses
- Cytokine profile (IL-5, IL-6, and soluble IL-2 receptor)
- Genetic testing for immunodeficiency syndromes

Though all the five classes of immunoglobulin heavy chain isotypes can be increased in polyclonal gammopathy, a relative increase of specific subtypes can help narrow the possible differentials. Impaired B cell immunoglobulin class

switching is associated with a polyclonal increase in IgM concentration.[17][18]

Acute infection and hyper-IgM syndrome also result in elevated serum IgM concentration.[19]

Liver cirrhosis is usually associated with a polyclonal increase in IgA concentration. Polyclonal increases in IgA levels are also seen in IgA vasculitis (Henoch Schoenlein purpura), IgA nephropathy, autoimmune diseases (e.g., rheumatoid arthritis, celiac disease, and systemic lupus erythematosus), and AIDS (Acquired immunodeficiency syndrome).

Most cases of hyper-IgD syndromes also have elevated IgA levels (commonly associated with MVK mutation).[20] More recently, an increased concentration of IgA has been reported in severe covid-19 pneumonia.[21]

Increased serum IgE level is associated with atopic disease, lymphoma, hyper-IgE syndrome (commonly associated with STAT3 mutations), and various allergic conditions.[22]

An increased IgG concentration is associated with liver disease, autoimmune disease, vasculitis, infection, hematological disease, IgG4-related disease, immunodeficiency, and iatrogenic (from intravenous immunoglobulin administration).[4]

Treatment / Management

Initial management of hypergammaglobulinemia (polyclonal gammopathy) involves evaluating the underlying disease. Since there is no specific therapy for hypergammaglobulinemia (polyclonal gammopathy), treatment is directed at the primary disorder. In most cases, treatment of the primary condition leads to the resolution of hypergammaglobulinemia (polyclonal gammopathy).[2]

Hyperviscosity syndrome secondary to hypergammaglobulinemia (polyclonal gammopathy) can be treated with systemic corticosteroid and plasmapheresis.[23][24]

For hypergammaglobulinemia (polyclonal gammopathy) associated with IgG4-related disease, corticosteroids and rituximab are used as first-line therapy.[25] Most patients (approximately 80%) respond well to oral or parenteral corticosteroids. Key recommendations are to start prednisolone at 0.5 to 1.0 mg per kg of body weight for 3 to 4 weeks, then taper the dose gradually.[3]

The efficacy of rituximab is better than corticosteroids. Approximately 95% of patients with hypergammaglobulinemia (polyclonal gammopathy) associated with IgG4-related disease will respond satisfactorily to rituximab.[3][26]

Key recommendations are to induce remission with intravenous rituximab first, then maintenance therapy with low dose corticosteroids or steroid-sparing agent, and follow up with monthly bloodwork. The preferred dose to induce remission is 1 g of rituximab intravenously twice two weeks apart. Once the remission is achieved, monthly follow-up with total IgG, IgG subclass, and serum protein electrophoresis is recommended.

Critical organ damage markers such as c-reactive protein, liver enzymes, and lipase should also be checked routinely. Most of the patients remain in remission with low-dose prednisone. Steroid-sparing agents such as mycophenolate mofetil or azathioprine are preferred to avoid long-term corticosteroid-related side effects. Many patients relapse within one year and need retreatment with rituximab. Although there is no standard therapy in life-threatening cases, combination therapy with fludarabine and rituximab has been used successfully in the cases of treatment-resistant diseases.[27]

Patients with immune thrombocytopenia, autoimmune hemolytic anemia, and other immune cytopenias should have baseline quantitative immunoglobulin and serum protein electrophoresis testing to rule out other conditions such as common variable immune deficiency and autoimmune lymphoproliferative syndrome. Both common variable

immune deficiency and autoimmune lymphoproliferative syndrome may present with polyclonal hypergammaglobulinemia.[4]

Severe chronic inflammation from hidradenitis suppurativa and human herpes virus 8 negative idiopathic multicentric Castleman disease is treated with anakinra (IL-1 inhibitor) and siltuximab (IL-6 inhibitor), respectively.

Hypergammaglobulinemia secondary to Sjogren syndrome can be observed periodically without any specific treatment.[4]

Differential Diagnosis

The differential diagnosis of 'hypergammaglobulinemia (polyclonal gammopathy)' is broad. When 'hypergammaglobulinemia (polyclonal gammopathy)' is found on serum protein electrophoresis, the following differentials should be considered.[2]

Liver Disease

It is the single most common cause of hypergammaglobulinemia (polyclonal gammopathy).[2]

- Autoimmune hepatitis
- Viral hepatitis
- Ethanol-induced liver injury
- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)
- Cryptogenic cirrhosis
- Primary hemochromatosis
- Alpha1-Antitrypsin deficiency (A1AT deficiency)

Connective Tissue Disease

- Sjogren syndrome
- Systemic lupus erythematosus (SLE)
- Rheumatoid arthritis (RA)
- Mixed connective tissue disease (MCTD)
- Overlap syndrome
- Familial Mediterranean fever (FMF)
- Benign hypergammaglobulinemic purpura of Waldenstrom
- Juvenile rheumatoid arthritis
- Temporal arteritis
- Cutaneous vasculitis
- CREST syndrome (Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia)

- Inclusion body myositis
- Progressive systemic sclerosis
- Ankylosing spondylitis
- Raynaud phenomenon
- Eosinophilic fasciitis
- Cryoglobulinemia

Lymphoproliferative Disorders

- Pseudo-lymphoma
- Malignant lymphoma
- Castleman disease (a group of uncommon lymphoproliferative disorders)
- Large granular lymphocytic leukemia (LGL)
- Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD)
- Chronic lymphocytic leukemia (CLL)
- Histiocytosis X
- Hairy cell leukemia (HCL)
- Plasma cell leukemia (PCL)
- Sinus histiocytosis with massive lymphadenopathy (SHML)
- Kikuchi disease (histiocytic necrotizing lymphadenitis)
- Cutaneous eruptive histiocytoma
- Systemic cutaneous plasmacytosis
- Severe autoimmune lymphoproliferative syndrome (ALPS)
- Intracranial plasma cell granuloma
- Proteinaceous lymphadenopathy with hypergammaglobulinemia
- Chronic active Epstein-Barr virus (EBV) infection

Myelodysplastic syndromes

Nonhematologic Malignancy

- Gastric carcinoma
- Hepatocellular carcinoma
- Lung cancer
- Renal cell carcinoma
- Chondrosarcoma

- Ovarian cancer

Infections

- Subacute bacterial endocarditis
- Whipple disease
- Brucellosis
- Lyme disease
- Renal abscess
- Cystic fibrosis
- *Mycobacterium tuberculosis*
- *Mycobacterium leprae*
- *Trypanosoma cruzi*
- *Toxocara canis*
- *Leishmania* organisms
- Human immunodeficiency virus 1
- Covid-19 (lancet pdf ref 10)
- Varicella
- Vaccinia

Neurologic Conditions

- Acquired chronic dysimmune demyelinating polyneuropathy
- Chronic progressive sensory ataxic neuropathy
- HTLV-1–associated myelopathy
- Microangiopathy of vasa nervorum in dysglobulinemic neuropathy
- Pure motor neuron disease and plasma cell dyscrasia

Diseases with Associated Immune System Aberrance

- Graves disease
- Chronic ulcerative colitis
- Sarcoidosis
- Chronic autoimmune pancreatitis
- Hyperimmunoglobulinemia D and periodic fever syndrome
- Syndrome of IgG2 subclass deficiency

Other Hematologic Conditions

- Idiopathic thrombocytopenic purpura (ITP)
- Idiopathic neutropenia
- Severe hemophilia A
- Sickle cell anemia
- Thalassemia major
- Fanconi anemia

Miscellaneous Conditions

- Cardiac myxoma
- Asbestos exposure
- Lymphoid interstitial pneumonia (LIP)
- Cryptogenic organizing pneumonitis (COP)
- Distal renal tubular acidosis (dRTA)
- Gaucher disease
- Meniere disease

Prognosis

Most cases of 'hypergammaglobulinemia (polyclonal gammopathy)' resolve after treating the primary disease. There is no definitive way of predicting outcomes in an individual patient. However, age, disease group, serum albumin concentration, and platelet count are significant predictors of survival.[2]

Complications

Patients with 'hypergammaglobulinemia (polyclonal gammopathy)' are at increased risk of secondary infections. Also, some reports of hyperviscosity syndrome are associated with 'hypergammaglobulinemia (polyclonal gammopathy).'[28]

Deterrence and Patient Education

Patient education is a vital part of managing hypergammaglobulinemia (polyclonal gammopathy). The patient needs to understand that hypergammaglobulinemia (polyclonal gammopathy) is not a malignant condition and regular monitoring of serum protein electrophoresis is a crucial part of management. In addition, the patient's active participation in decision-making helps improve compliance.

Pearls and Other Issues

Although rare, some reports on IgG4-related disease mimicking plasma cell myeloma and vice versa are reported.[29] [30] Furthermore, polyclonal gammopathy resulting from an increased serum IgG4 level can resemble monoclonal gammopathy on serum protein electrophoresis.[31] So, the clinician needs to interpret serum protein electrophoresis and IgG subclass testing.

Hypergammaglobulinemia (polyclonal gammopathy) can also cause false positive HIV serology in chronic granulomatous disease (CGD) and other inborn errors of immunity.[32] A decreased anion gap is often seen in a

patient with Hypergammaglobulinemia (polyclonal gammopathy) associated with hypoalbuminemia.[33] False positive direct antiglobulin test can also be associated with Hypergammaglobulinemia (polyclonal gammopathy).[34]

Enhancing Healthcare Team Outcomes

Hypergammaglobulinemia (polyclonal gammopathy) is a complex disease process and requires communication between primary clinicians, internists, hematologists, pathologists, and other healthcare providers for early evaluation and management of the patient. From a diagnostic point of view, a pathologist will provide an interpretation of serum protein electrophoresis.

A hematologist may give an expert opinion regarding the possible association with monoclonal gammopathy or any other hematological disorder. A primary clinician and an internist will help manage and follow up on the underlying condition causing hypergammaglobulinemia (polyclonal gammopathy). The psychological and financial implications of chronic disease should also be considered.

Review Questions

- Access free multiple choice questions on this topic.
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