Monoclonal Gammopathy in Medical Diseases

An Essay
Submitted for Partial Fulfillment of Master Degree in
Internal Medicine

By

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List of abbreviations

ALS	Amyotrophic lateral sclerosis
ASCT	Autologous SCT
CEV	cyclophosphamide, etoposide, epirubicin
CI	Confidence Interval
CIDP	chronic inflammatory demyelinating polyneuropathy
CMI	cell-mediated immunity
CMV	Cytomegalovirus
CRAB	hypercalcemia, renal insufficiency, anemia, and bone lesions
CVCs	central venous catheters
DADS	Distal acquired symmetric demyelinating neuropathy
del(13)	deletions in chromosome 13
Dex	Dexamethasone
EFS	event-free survival
EP	Extramedullary plasmacytomas
FLC	free light chain
GAG's	Glycosaminoglycans
HCV	hepatitis C virus
HDM	High-dose melphalan
HSV	herpes simplex virus
HLA	human leukocyte antigen
IGLV1	immunoglobulin light chain variable gene
IL-6	interleukin-6
IMiDs	immunomodulatory drugs
IVIG	intravenous immunoglobulin
LCDD	light chain deposition disease
LDH	lactate dehydrogenase
LPD	lymphoproliferative disorders
M protein	monoclonal protein
MAG	Myelin-associated glycoprotein

MAPK	mitogen-activated protein kinase
MBD	Myeloma bone disease
MC	mixed cryoglobulinemia
MDS	Myelodysplasia
MG	monoclonal gammopathy
MGUS	monoclonal gammopathy of undetermined significance
MIDD	monoclonal Ig deposition disease
MIP	macrophage inflammatory protein
MM	Multiple myeloma
MND	motor neuron disease
MPT	melphalan, prednisone, and thalidomide
MS	mass spectrometry
NA	not applicable
nCR	near-complete response
NF-κB	nuclear factor-κB
OBs	Osteoblasts
OC	Osteoclast
ORR	Overall response rates
OS	Overall survival
PAD	bortezomib, adriamycin, dexamethasone
PBSCs	peripheral blood stem cells
PCLI	plasma cell labeling index
PCs	plasma cells
PET	positron emission tomography
PFS	progression-free survival
PJP	Pneumocystis jirovecii pneumonia
PN	Peripheral neuropathy
ROTI	related organ or tissue impairment
PPN	Paraproteinemic neuropathy
RANKL	receptor activator of nuclear factor _B ligand
RR	relapsed/refractory
SAP	serum amyloid P

SBP	solitary bone plasmacytoma
SCT	stem cell transplant
SD	stable disease
SFLC	serum free light chains
SFN	Small fiber neuropathy
SGPG	Sulfoglucuronyl paragloboside
SLE	systemic Lupus erythematosus
SMM	smoldering MM
SPEP and UPEP	serum and urine protein electrophoresis
SS	Sjögren syndrome
t(4;14)	translocation between chromosome 4 and 14
Thal	Thalidomide
TMA	thrombotic microangiopathy
TNF	tumor necrosis factor
TTP	time to progression
VAD	vincristine, Adriamycin ,dex
VCD	bortezomib, cyclophosphamide, dexamethasone
VEGF	vascular endothelial growth factor
VGPR	very good partial response
VTD	bortezomib,thalidomide, dexamethasone
VTD-PACE	bortezomib ,thal, dex, cisplatin, doxorubicin, cyclophosphamide, and etoposide
VTE	Venous thromboembolism
VZV	varicella-zoster virus
WHO	World Health Organization
WM	Waldenström's macroglobulinemia

Introduction and Aim of the work

Monoclonal gammopathy or paraproteinemia is the presence of excessive amounts of a single monoclonal gammaglobulin in the blood. It denotes an underlying immunoproliferative disorder. It is considered equivalent to plasma cell dyscrasia. **(Cook and Macdonald, 2007)**

The most common plasma cell dyscrasia is monoclonal gammopathy of undetermined significance (MGUS); closely related disorders include multiple myeloma, solitary plasmacytoma of bone, extramedullary plasmacytoma, Waldenström's macroglobulinemia (WM), primary amyloidosis, and heavy-chain disease. The spectrum of MGUS, solitary plasmacytoma of bone, and asymptomatic and symptomatic multiple myeloma may actually represent a natural progression of the same disease. **(Tedeschi et al., 2007)**

Monoclonal gammopathy of undetermined significance (MGUS) denote the presence of a monoclonal immunoglobulin (Ig), also called an M-protein, in the serum or urine in persons without evidence of multiple myeloma (MM), Waldenström macroglobulinemia (WM), amyloidosis (AL) or other lymphoproliferative disorders.**(Bida et al.,2009)**

In 2009, prospective data demonstrated that all or almost all cases of Multiple Myeloma are preceded by MGUS. In addition to multiple myeloma, MGUS may also progress to Waldenström's macroglobulinemia, primary amyloidosis, B-cell lymphoma, or chronic lymphocytic leukemia**.(Landgren et al.,2009)**

Non-malignant disorders associated with monoclonal proteins (usually MGUS) include peripheral neuropathy, renal failure, autoimmune diseases (polymyositis/dermatomyositis, systemic sclerosis, SS, autoimmune hemolytic anemia, pernicious anemia, and ankylosing spondylitis) dermatological diseases such as lichen myxoedematosus (IgG1), scleroderma, pyoderma gangrenosum, necrobiotic xanthogranuloma, discoid lupus erythematosus, psoriasis, cutaneous lymphoma and also liver diseases such as chronic hepatitis, cirrhosis, primary biliary cirrhosis and miscellaneous such as rheumatoid arthritis, inflammatory seronegative polyarthritis, polymyositis (IgGκ), polymyalgia rheumatica, myasthenia gravis, angioneurotic oedem. **(Hemminki et al., 2006)**

The initial laboratory evaluation of the monoclonal gammopathies relies on serum and urine protein electrophoresis and the serum free light chain assay. Agarose gel electrophoresis is the usual method of screening for M-protein with immunofixation performed to confirm its presence and to determine its immunoglobulin heavy chain class and light chain type. Quantification of immunoglobulins may be performed by nephelometry, but densitometry of the M-protein is preferred**.(Dispenzieri et al.,2009)**

Myeloma patients with a preceding diagnosis of MGUS have a better outcome in terms of survival and major complications (fractures and dialysis-dependent renal failure) compared with those who don't. **(Kyle et al., 2006)**

Some studies are assessing the effects of medications that are intended to reduce the risk of progression in patients with high-risk MGUS (i.e., a high serum monoclonal protein concentration, an immunoglobulin type other than IgG, and an abnormal free light-chain ratio).**(Blade and Rosinol,2006)**

Aim of The Work

To study the monoclonal gammopathy in medical diseases and its impact on diagnosis and prognosis.

Methods

Review of recent medical literature and journals regarding monoclonal gammopathy in medical diseases.

Monoclonal gammopathy

Monoclonal gammopathy or paraproteinemia is the presence of excessive amounts of a single monoclonal gammaglobulin ("paraprotein") in the blood. It denotes an underlying immunoproliferative disorder, it is considered equivalent to plasma cell dyscrasia. **(Cook and Macdonald, 2007)**

Plasma cell disorders (plasma cell dyscrasias) are uncommon. They begin when a single group (clone) of plasma cells multiplies excessively and produces a large quantity of a single type of antibody. Plasma cells develop from B lymphocytes, a type of white blood cell that normally produces antibodies, which help the body fight infection. Plasma cells are present mainly in bone marrow and lymph nodes. Every plasma cell divides repeatedly to form a clone, composed of many identical cells. The cells of a clone produce only one specific type of antibody. Because thousands of different clones exist, the body can produce a vast number of different antibodies to fight the body's frequent exposure to infectious microorganisms. **(James, 2008)**

In plasma cell disorders, one clone of plasma cells multiplies uncontrollably. As a result, this clone produces vast amounts of a single antibody (monoclonal antibody) known as the M-protein. In some cases (such as with monoclonal gammopathies), the antibody produced is incomplete, consisting of only light chains or heavy chains .These abnormal plasma cells and the antibodies they produce are limited to one type, and levels of other types of antibodies that help fight infections fall**. (Dispenzieri et al.,2009)**

People with plasma cell disorders are often at higher risk of infections. The ever-increasing number of abnormal plasma cells also invades and damages various tissues and organs, and the antibody produced by the clone of plasma cells can sometimes damage vital organs, especially the kidneys and bones. **(James, 2008)**

A paraprotein is a monoclonal immunoglobulin or immunoglobulin light chain (Bence Jones protein) present in the blood or urine and arising from clonal proliferation of plasma cells. Alternative terms include monoclonal protein or M-band. Paraproteins are characterised by homogenous electrophoretic migration and the expression of a single light chain type, either κ or λ.At one extreme there may be an overtly malignant clonal proliferation of plasma cells resulting in multiple myeloma, or

solitary plasmacytoma (skeletal or extramedullary.) At the other extreme there may be a low level paraprotein ultimately classified as monoclonal gammopathy of undetermined significance (MGUS) which may be of little clinical relevance. **(Kyle et al.,2006)**

The incidence of paraproteinaemia in the general population. In individuals aged >50 years; the overall a varies with age (age 50–59, 1.7%; age >70, 5.3%) and sex (men: women, 4.0%: 2.7%.). Prevalence of MGUS being threefold higher in African Americans than the white population. Paraproteins are therefore a common laboratory finding in an elderly population. (**Landgren et al., 2006)**

Types of paraproteinemias

Paraproteinemias may be categorized according to the type of monoclonal protein found in blood :

1-Light chains only (also known as "AL amyloidosis or "light chain disease").

2-Heavy chains only (also known as "heavy chain disease").

3-Whole immunoglobulins (albeit often with an abnormal light / heavy chain ratio)