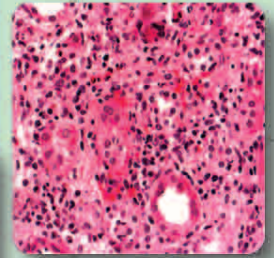
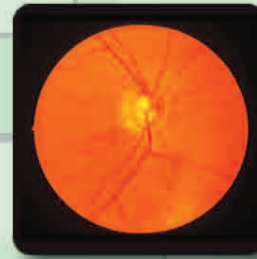


the **S Q U A R E**

Healthcare **bulletin**



- ▣ *Drug-Induced Kidney Injury*
- ▣ *Glaucoma*
- ▣ *Multiple Myeloma*
- ▣ *Middle East Respiratory Syndrome*



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34

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Contents

<i>Drug-Induced Kidney Injury</i>	Page 01
<i>Glaucoma</i>	Page 04
<i>Multiple Myeloma</i>	Page 09
<i>Middle East Respiratory Syndrome</i>	Page 19

Editorial



Dear Doctor

It gives us great pleasure to introduce this latest edition of "the SQUARE" healthcare bulletin!

In this issue we bring you the details on "Drug - Induced Kidney Injury" that constitutes an important cause of acute renal failure and chronic kidney disease in present day clinical practice. The incidence of drug-induced nephrotoxicity has been increasing with the ever increasing number of drugs and with easy availability of over-the-counter medications. A basic understanding of drug induced renal injury will help to better understand drug-induced renal toxicity and allow for a vigilant approach when prescribing drugs with potential renal toxicity. A topic on "Glaucoma" which is the leading cause of irreversible blindness in the world has been included in this issue. We have also published a feature on "Multiple Myeloma" that affects thousands of people worldwide and is the second most common cancer of the blood only to non-Hodgkin's lymphoma. Multiple myeloma accounts for around 1% of all cancers worldwide and for about 2% of cancer-related deaths. Besides, we have highlighted on "Middle East Respiratory Syndrome(MERS)", a disease caused by a new virus that causes a rapid onset of severe respiratory disease in people. As of 26 March 2014, the WHO had received reports of 206 laboratory-confirmed cases of MERS-CoV, including 86 deaths. The World Health Organization (WHO), CDC and other partners are working to better understand the possible risks from MERS-CoV to the public's health.

We hope that you will find this newsletter both interesting and informative. On behalf of the management of *SQUARE*, we wish you and your family a healthy and blissful life!

Thank you!



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At present, there is changing trends of disease pattern. The number of elderly people with chronic diseases has been increasing, many of which, also suffer from various co-morbid illness. So, people are now exposed to more diagnostic procedures and multiple medications. As the kidneys receive a rich blood flow of 25% of resting cardiac output and play an important role in the elimination of many drugs and their metabolites, they are vulnerable to injury by drugs. Although renal impairment is often reversible if the offending drug is discontinued, drugs are well-known cause of end-stage renal disease (ESRD). Therefore, successful prevention of drug-induced kidney injuries requires knowledge of risk factors, pathogenic mechanisms of injury and pre-emptive measures coupled with early intervention.

Risk factors

Drug-induced kidney injury tends to occur more frequently in certain patients and with certain drugs in many clinical situations. So, these factors can be divided into patient-related risk factors & drug-related risk factors.

a. Patient-related risk factors

Patient-related risk factors vary somewhat depending upon the offending drug. However, some risk factors are common to all nephrotoxic drugs. These are mentioned in table 1.

Table 1: Patient-related risk factors :

- ❑ Absolute or effective intravascular volume depletion
- ❑ Age older than 60 years
- ❑ Underlying renal insufficiency (e.g., GFR < 60 mL/ min/1.73m²)
- ❑ Simultaneous exposure to multiple nephrotoxic drugs
- ❑ Diabetes mellitus
- ❑ Congestive heart failure
- ❑ Sepsis

There are conflicting reports about the influence of race and genetic variation, as well as whether men are at greater risk of developing acute renal failure compared with women. The risk of acute renal failure increases with the presence of each additional risk factor.

b. Drug-related risk factors

Certain drugs are inherently nephrotoxic. These include aminoglycosides, cisplatin, amphotericin B, contrast dye, ciclosporin and tacrolimus. For others, such as those associated with interstitial nephritis and crystal deposition, renal injury is dose-dependent or related to prolonged duration of treatment. Combination therapy with multiple nephrotoxins can result in synergistic renal injury. Patient-related factors also play significant role to potentiate drug-related kidney injury.

Pathogenesis

Nephrotoxic drugs exert their toxic effects on the kidneys by one or more common pathogenic mechanisms. These may cause predictable, cumulative dose-dependent toxicity or idiosyncratic dose-indepen-

dent toxicity at any time during therapy. Cumulative dose-dependent toxicity can be anticipated and prevented, but idiosyncratic toxicity cannot be anticipated. Injury may occur in various compartments of kidneys e.g., the glomerulus, the renal vascular supply, the tubulointerstitium and the collecting ducts.

❑ Glomerular injury

The glomerulus is a specialized structure which is composed of cells (epithelial, mesangial, endothelial) and matrix (mesangium, basement membrane) in a complex network of capillaries. Injury to these various components of the glomerulus produces more specific clinical syndromes. Altered intra-glomerular hemodynamics, podocyte injury, immune-complex glomerulonephritis, glomerular endothelial injury are several types of glomerular injuries.

The kidneys autoregulate intra-glomerular pressure by modulating the afferent and efferent arteriolar tone to preserve GFR and urine output. Angiotensin-II and prostaglandins play important role in this regard. So, drugs that act as anti-prostaglandins (NSAIDs) or those with anti-angiotensin II activity (ACEI or ARB) can interfere with the kidneys' ability to autoregulate glomerular pressure and thus decrease GFR.

Since 1980s, an important association of NSAIDs with minimal change disease has been known. Podocyte injury may occur with effacement of foot process and accompanying abnormal filtration slit. COX-2 inhibitors, interferons, lithium, pamidronate are also implicated in podocyte injury. Nephrotic syndrome or FSGS may result in.

❑ Tubulo-interstitial injury

This comprises immune-mediated tubulo-interstitial inflammation, analgesic nephropathy, toxic cytopathies and many others.

Immune-mediated mechanism is the most common of this type of injury. Antibiotics and analgesics probably account for a significant proportion of these cases. Antibiotics can produce a systemic hypersensitivity reaction and NSAIDs trigger a cell-mediated or delayed-type hypersensitivity response. Tissue eosinophilia is common and eosinophilia is a screening test for acute allergic interstitial nephritis. Proton-pump inhibitors are continuously being recognized as contributing to acute interstitial nephritis. Another mechanism implicated is the formation of immune complexes where drugs act as haptens. Many drugs can induce a granulomatous reaction. So, both acute and chronic interstitial nephritis are encountered.

A more severe form of kidney damage termed analgesic nephropathy may be seen when combination analgesics are used in large cumulative doses. The drug combinations usually refer to paracetamol and aspirin/other NSAIDs. Aminoglycosides have long been known to be nephrotoxic where tubular injury seems the most likely explanation. Lithium, prescribed for the treatment of bipolar disorders, can cause nephrogenic diabetes insipidus possibly resulting from down-regulation of aquaporin-2 expression in the collecting duct. With long-term use of lithium, chronic tubulointerstitial nephritis and tubular microcytosis may occur. Cisplatin and carboplatin, used as anti-cancer drug, can cause dose-related direct cellular toxicity. Osmotic nephrosis may result from use of plasma volume expanders, mannitol, sucrose-rich IVIG.

❑ Vascular injury

Extraglomerular vascular injury is not uncommon. Calcineurin inhibitors (cyclosporin & tacrolimus) cause dose-dependent vasoconstriction of the afferent arterioles, leading to renal impairment in at-risk patients. The lesions can be seen from days to several weeks after the onset of treatment. The earliest abnormalities are injuries to the endothelial cells and myocytes with resultant swelling and nodular hyalinosis. Thrombotic microangiopathy is seen in more severe instances of calcineurin inhibitors toxicity which can lead to vascular occlusion and parenchymal ischemia. Sirolimus and OKT3 (anti-CD3 monoclonal antibody) are both associated with thrombotic microangiopathy. Cocaine and the substances that cause thrombosis in glomeruli can also produce thrombotic microangiopathy. Inflammatory vasculitis secondary to the effects of drugs is generally uncommon.

❑ Injury due to crystallization

There are chemical agents and medications that cause kidney damage by forming crystalline deposits, resulting in tubular injury, interstitial inflammation and obstruction. The drugs or their metabolites crystallize when they become supersaturated in the urine. Dehydration is an important contributing factor. Hypercalcemia due to excess vitamin D causes deposition of calcium phosphate. Consuming large quantities of vitamin C and star fruit juice allow calcium oxalate crystals to form. Many drugs induce hyperuricemia (alcohol, thiazides, furosemide, cisplatin, cyclosporin) and the chemotherapeutic agents may trigger a 'tumor lysis syndrome', causing uric acid nephropathy. Sulfa drugs, aciclovir and indinavir have all been associated with tubular crystallopathy, urolithiasis and interstitial nephritis. Acute nephrocalcinosis following the use of oral sodium phosphate solutions for colonoscopy result from calcium phosphate crystallization.

Drug-induced renal syndromes

From the clinical point of view, it may be more useful to classify drug-induced kidney injury into some major syndromes: acute renal failure, chronic renal failure & nephrotic syndrome.

❑ Nephrotic syndrome

Nephrotic syndrome is caused by glomerular dysfunction and is marked by heavy proteinuria. Minimal change disease and focal segmental glomerulosclerosis are primarily encountered. NSAIDs, lithium, pamidronate, interferons alpha & beta are implicated. NSAIDs, captopril and penicillamine may also cause membranous glomerulonephritis.

❑ Acute renal failure

Drugs cause approximately 20 percent of community- and hospital-acquired episodes of acute renal failure. Among the older adults, the incidence of drug-induced nephrotoxicity may be as high as 66 percent. Drugs can cause dose-dependent acute renal failure by causing pre-renal, intrinsic or post-renal toxicity. Pre-renal ARF is caused by impairing glomerular hemofiltration by modulating the vasomotor tone of the afferent or efferent arterioles. Patients who already have compromised renal perfusion are most at risk. Low urine

output with high osmolality is characteristic. Parenchymal drug-induced renal injury may occur in the form of acute tubular necrosis, interstitial nephritis or thrombotic angiopathy. Low urine output and urinary sediment containing granular casts and epithelial cells are common. Many drugs can also cause crystal-induced acute obstructive uropathy. All conditions are associated with rapid rise of serum creatinine level. Drugs causing ARF by various means are mentioned in table 2.

Table 2: Drugs causing ARF

Pre-renal	NSAIDs, ACEI, ARB, Diuretics, Cyclosporin, Tacrolimus
Intrinsic	<ul style="list-style-type: none"> ● Acute tubular necrosis : Aminoglycosides, Amphotericin B, Cisplatin, Radio-contrast media ● Tubulointerstitial nephritis: Penicillins, Cephalosporins, Sulfonamides, Quinolones, NSAIDs, Thiazides, Lithium, Proton pump inhibitors, Allopurinol, Anti-epileptics ● Thrombotic microangiopathy: Cyclosporin, Tacrolimus, Anti-cancer drugs, Estrogens, Clopidogrel, Quinine
Obstructive	Aciclovir, Sulfonamides, Methotrexate, Ciprofloxacin, Sodium phosphate

❑ Chronic renal failure

Drug-induced chronic renal failure presents with a slowly progressive elevation of serum creatinine level. There is microscopic tubulointerstitial nephritis which is characterized by interstitial fibrosis, tubular atrophy and inflammation. Many of the chronic forms result from repeated or prolonged episodes of acute tubulointerstitial nephritis. Only a few drugs such as, NSAIDs and lithium are associated with chronic renal failure.

Biochemical evidence of kidney injury

A decrease in renal function as evidenced by a rise in serum creatinine levels following the initiation of a drug signals the possibility of drug-induced renal injury. Although there are no standard guidelines used to interpret changes in serum creatinine, a 50 percent rise from baseline, an increase of 0.5 mg/dL or more when baseline serum creatinine is less than 2 mg/dL or an increase of 1 mg/ dL or more if baseline creatinine is greater than 2 mg per dL have been used as biochemical criteria of acute renal failure.

Prevention

At-risk patients should be closely monitored for changes in renal function when a medication is added or a dosage is increased. Most drugs that are eliminated renally do not require dosage adjustment until the creatinine clearance falls below 50 mL/ min. At the first sign of renal dysfunction, the patient's medication list should be reviewed to identify offending agents. If multiple medications are present and the patient is clinically stable, the drug most recently added to the patient's medication regimen should be discontinued.

Attention should be directed at avoiding further renal insults by supporting blood pressure, maintaining adequate hydration and temporarily discontinuing all other possible nephrotoxins.

General preventive measures are mentioned in table 3.

Table 3: General measures for the prevention of drug-induced kidney injury include:

- Assessment of baseline renal function before initiating therapy
- Correction of risk factors before prescribing drugs
- Adjustment of the dose of medications according to the status of renal function
- Avoidance of combination of potentially nephrotoxic drug.
- Use of equally effective but non-nephrotoxic drugs whenever possible
- Adequate hydration is important to maintain renal perfusion and avoid drug-induced renal impairment.
- Careful monitoring of serum creatinine levels after starting or increasing the dosage of drugs with potential for nephrotoxicity.

Kidney injury by commonly prescribed drugs with preventive measures

□ ACEIs/ARBs

These agents may reduce glomerular perfusion pressure and GFR. Serum creatinine level may be increased after initiation of therapy. Volume depletion must be corrected before initiation of drug, especially if used on a chronic basis and with diuretics. Monitoring of renal function and vital signs following initiation or dose escalation should be carried out, especially if used in at-risk patients. These drug classes are contraindicated in renal artery stenosis and pregnancy.

□ NSAIDs

NSAIDs are associated with alteration of intraglomerular hemodynamics, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis leading to chronic kidney disease and recently found glomerulonephritis. The longer the duration of use of these drugs, the more severe is the injury. Analgesics with less anti-prostaglandin activity such as paracetamol, aspirin, sulindac should be used if possible. Volume depletion must be corrected before initiation of NSAIDs. Renal function and vital signs should be monitored in vulnerable patients. Long-term use should be avoided. Alternative agents should be used in patients with chronic pain.

□ Aminoglycosides

Histopathological studies strongly support the concept that tubular necrosis is the primary cause of functional renal toxicity by aminoglycosides. Moreover, inappropriate activation of the renin-angiotensin system and the ensuing local vasoconstriction appear to be primarily responsible for the decrease in glomerular filtration. To prevent renal injury by these agents, extended-interval dosing regimen (e.g., once daily) should be used. Administration during the active

period of day is less-harmful. Duration of therapy should be minimized. Trough levels 1 mcg/mL should be maintained. Monitoring of renal function two to three times per week or daily in severely ill patients should be carried out. Special caution should be exercised when these agents are used concomitantly with other potentially nephrotoxic agents e.g., NSAIDs, loop diuretics, penicillins, cephalosporins etc.

□ Other antibiotics

Penicillins and cephalosporins may cause generalized allergic hypersensitivity reaction that can involve kidneys. Acute interstitial nephritis and glomerulonephritis are the pathogenic mechanisms. Sulfonamides, vancomycin, rifampicin and quinolones may also cause acute interstitial nephritis. Crystal associated nephropathy may result from the use of sulfonamides and ciprofloxacin. Careful selection of patients and adequate hydration are essential to prevent renal injury by these agents.

□ Radio-contrast agents

These are used to improve the visibility of internal bodily structures in X-ray based imaging techniques such as computed tomography (CT) and radiography in various conditions e.g., angiography, venography, urography, hysterosalpingography etc. Ionic (iodine-containing) contrast media typically, but not always, have higher osmolality and more side-effects. In addition to anaphylactoid reactions, these agents are also familiar for contrast-induced nephropathy. Contrast-induced acute tubular necrosis and acute tubulointerstitial nephritis are the main pathogenic mechanisms. To prevent this, prior screening of baseline renal function and health status of the patients are essential. Low-osmolar contrast agent in the lowest possible dose should be used. Multiple procedures in a 24 to 48 hours' period should be avoided. Normal saline or sodium bicarbonate (154 mEq/L) infusion before and after procedure can wash out contrast agents rapidly. Concurrent use of NSAIDs and diuretics should be withheld for at least 24 hours before and after procedures. Monitoring of renal function 24 to 48 hours post-procedure should be done. N-acetylcysteine (600-1200 mg PO) on the day before and of the procedure may reduce nephropathy. Methylxanthines may help although studies have conflicting results.

□ Other drugs

Rhabdomyolysis by statins, haloperidol, opioids may follow acute renal failure. Proton-pump inhibitors, ranitidine, loop diuretics and allopurinol are associated with acute interstitial nephritis. Clopidogrel and quinine may cause thrombotic microangiopathy. Anticancer drugs, bisphosphonates, amphotericin B are associated with tubular cell injury.

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The term glaucoma goes back to hippocratic times. Its meaning is disputed; generally accepted to signify greenish - like the colour of sea water - Hirschberg has shown that it is much more likely to mean bluish. It would appear that in Hippocratic writings hypochyma and glaucosis were synonym. Glaucoma is a term describing a group of ocular disorders with multifactorial etiology united by a clinically characteristic intraocular pressure-associated optic neuropathy. This can permanently damage vision in the affected eyes and lead to blindness if untreated. It is normally associated with increased fluid pressure in the eye. The term "ocular hypertension" is used for the people with consistently raised intraocular pressure (IOP) without any associated optic nerve damage. Conversely, the term 'normal tension' or 'low tension' glaucoma is used for those with optic nerve damage and associated visual field loss, but normal or low IOP.



Figure : Tunnel vision

The nerve damage involves loss of retinal ganglion cells in a characteristic pattern. The many different subtypes of glaucoma can all be considered to be a type of optic neuropathy. Raised intraocular pressure (above 21 mmHg or 2.8 kPa) is the most important and only modifiable risk factor for glaucoma. However, some may have high intraocular pressure for years and never develop damage, while others can develop nerve damage at a relatively low pressure. Untreated glaucoma can lead to permanent damage of the optic nerve and resultant visual field loss, which over time can progress to blindness.

Types

Glaucoma is the second most common cause of blindness in the world after cataract. There are several types of glaucoma :

- Open-angle glaucoma
- Angle-closure glaucoma
- Normal-tension glaucoma
- Secondary glaucoma
- Congenital glaucoma

Causes

Of the several causes of glaucoma, ocular hypertension is the most important risk factor in most glaucomas, but in some populations,

only 50% of people with primary open-angle glaucoma actually have elevated ocular pressure.

Dietary

No clear evidence indicates any dietary component cause glaucoma in humans.

Ethnicity and sex

Many people of East Asian descent are prone to developing angle closure glaucoma due to shallower anterior chamber depths. Inuit also have a 20 to 40 times higher risk of developing primary angle closure glaucoma. Women are three times more likely than men to develop acute angle closure glaucoma due to their shallower anterior chambers. People of African descent are three times more likely to develop primary open angle glaucoma.

Genetics

Positive family history is a risk factor for glaucoma. The relative risk of having primary open angle glaucoma (POAG) is increased approximately 2–4 fold for individuals who have a sibling with glaucoma. Glaucoma, particularly primary open angle glaucoma, is associated with mutations in several different genes (including MYOC, ASB10, WDR36, NTF4, TBK1 genes), although most cases of glaucoma do not involve these genetic mutations. Normal tension glaucoma, which comprises one-third of POAG, is also associated with genetic mutations (including OPA1 and OPTN genes).

Various rare congenital/genetic eye malformations are associated with glaucoma. Occasionally, failure of the normal third trimester gestational atrophy of the hyaloid canal and the tunica vasculosa lentis are associated with other anomalies. Angle closure-induced ocular hypertension and glaucomatous optic neuropathy may also occur with these anomalies and modelled in mice.

Others

Other factors can cause glaucoma, known as "secondary glaucomas", including prolonged use of steroids (steroid-induced glaucoma); conditions that severely restrict blood flow to the eye, such as severe diabetic retinopathy and central retinal vein occlusion (neovascular glaucoma); ocular trauma (angle recession glaucoma); and uveitis (uveitic glaucoma). In a large study in the UK, glaucoma patients had a 29% increased incidence of systemic hypertension compared to age- and sex-matched controls.

Risk factors

Certain factors can increase the risk for developing glaucoma. They include :

Age : People over age 60 years are at increased risk for the disease. For African Americans, however, the increase in risk begins after age of 40 years. The risk of developing glaucoma increases slightly with each year of age.

Race : African Americans are significantly more likely to get glaucoma than are Caucasians, and they are much more likely to suffer permanent vision loss as a result. People of Asian descent are at higher risk of angle-closure glaucoma and those of Japanese descent are more prone to low-tension glaucoma.

Family history of glaucoma : Having a family history of glaucoma increases the risk of developing glaucoma.

Medical conditions : Some studies indicate that diabetes may increase the risk of developing glaucoma, as do high blood pressure and heart disease.

Physical injuries to the eye : Severe trauma, such as being hit in the eye, can result in immediate increased eye pressure and future increases in pressure due to internal damage. Injury can also dislocate the lens, closing the drainage angle and increasing pressure.

Other eye-related risk factors : Eye anatomy, namely corneal thickness and optic nerve appearance indicate risk for development of glaucoma. Conditions such as retinal detachment, eye tumors and eye inflammations may also induce glaucoma. Some studies suggest that high amounts of nearsightedness may also be a risk factor for the development of glaucoma.

Corticosteroid use : Using corticosteroids for prolonged periods of time appears to put some people at risk of getting secondary glaucoma.

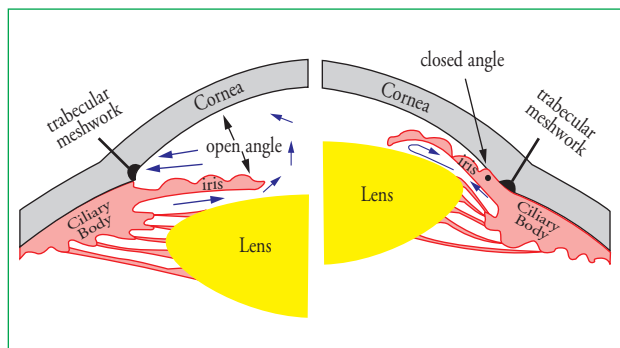


Figure : POAG and PACG

Pathophysiology

The underlying cause of open-angle glaucoma remains unclear. Several theories exist on its exact etiology.

In open/wide-angle glaucoma, flow is reduced through the trabecular meshwork, due to the degeneration and obstruction of the trabecular meshwork, whose original function is to absorb the aqueous humor. Loss of aqueous humor absorption leads to increased resistance and thus a chronic, painless buildup of pressure in the eye. In close/narrow-angle, the iridocorneal angle is completely closed because of forward displacement of the iris against the cornea, resulting in the inability of the aqueous fluid to flow from the posterior to the anterior chamber and then out of the trabecular network. This accumulation of aqueous humor causes an acute increase of pressure and pain.

The inconsistent relationship of glaucomatous optic neuropathy with ocular hypertension has provoked hypotheses and studies on anatomic structure, eye development, nerve compression trauma, optic nerve blood flow, excitatory neurotransmitter, trophic factor, retinal ganglion cell/axon degeneration, glial support cell, immune system, aging mechanisms of neuron loss and severing of the nerve fibers at the scleral edge.

Symptoms

Open-angle Glaucoma

- ❑ Most people have no symptoms
- ❑ Once vision loss occurs, the damage is already severe
- ❑ There is a slow loss of peripheral vision (also called tunnel vision)
- ❑ Advanced glaucoma can lead to blindness

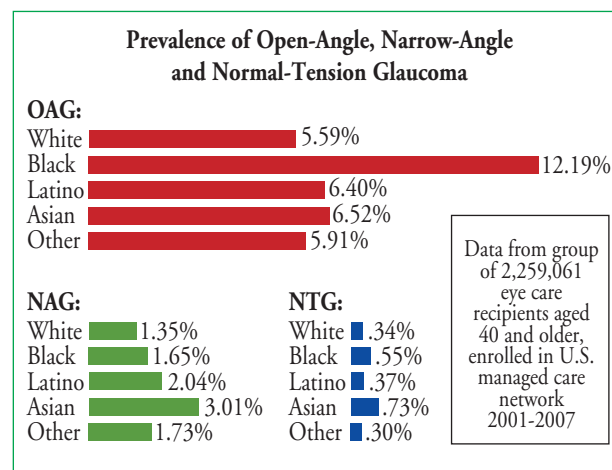


Figure : Prevalence of Glaucoma

Angle-closure Glaucoma

- ❑ Symptoms may come and go at first or steadily become worse
- ❑ Sudden, severe pain in the affected eye
- ❑ Decreased or cloudy vision, often called "steamy" vision
- ❑ Nausea and vomiting
- ❑ Rainbow-like halos around lights
- ❑ Red eye
- ❑ Eye feels swollen

Congenital Glaucoma

- ❑ Symptoms are usually noticed when the child is a few months old
- ❑ Cloudiness of the front of the eye
- ❑ Enlargement of one eye or both eyes
- ❑ Red eye
- ❑ Sensitivity to light
- ❑ Tearing

Epidemiology

As of 2010, there were 44.7 million people in the world with open angle glaucoma. In the same year, there were 2.8 million people in the United States with open angle glaucoma. By 2020, the prevalence is projected to increase to 58.6 million worldwide and 3.4 million in the United States.

Internationally, glaucoma is the second-leading cause of blindness, after cataracts. Glaucoma is also the leading cause of blindness in African Americans, who have higher rates of primary open angle glaucoma. Bilateral vision loss can negatively affect mobility and interfere with driving.

A meta-analysis published in 2009 found that patients with primary open angle glaucoma do not have increased mortality rates, or increased risk of cardiovascular death.

Diagnosis

An ophthalmologist can usually detect those individuals who are at risk for glaucoma before nerve damage occurs. The doctor also can diagnose patients who already have glaucoma by observing their nerve damage or visual field loss. The following tests, all of which are painless, may be part of this evaluation.

Tonometry : Determines the pressure in the eye by measuring the tone or firmness of its surface. Several types of tonometers are available for this test, the most common being the applanation tonometer. After the eye has been numbed with anesthetic eyedrops, the tonometer's sensor is placed against the front surface of the eye. The firmer the tone of the surface of the eye, the higher the pressure reading.

Pachymetry : Measures the thickness of the cornea. After the eye has been numbed with anesthetic eyedrops, the pachymeter tip is touched lightly to the front surface of the eye (cornea). Studies have shown that corneal thickness can affect the measurement of intraocular pressure. Thicker corneas may give falsely high eye pressure readings and thinner corneas may give falsely low pressure readings. Furthermore, thin corneas may be an additional risk factor for glaucoma. Once a doctor knows the thickness of a patient's cornea, he or she can more accurately interpret the patient's tonometry.

Gonioscopy : Done by numbing the eye with anesthetic drops and placing a special type of contact lens with mirrors inside the eye. The mirrors enable the doctor to view the interior of the eye from different directions. The purpose of this test is to examine the drainage angle and drainage area of the eye. In this procedure, the doctor can determine whether the angle is open or narrow and find any other abnormalities within the angle area. As indicated earlier, individuals with narrow angles have an increased risk for a sudden closure of the angle, which can cause an acute angle-closure glaucomatous attack. Gonioscopy can also determine whether the eye is subject to chronic angle closure, whether blood vessels are abnormal or whether hidden tumors might be blocking the drainage of the aqueous fluid out of the eye.

Ophthalmoscopy : This procedure is done to examine the optic nerve (seen as the optic disc) at the back of the eye. Damage to the optic nerve, called cupping of the disc, can be detected in this way. Cupping, which is an indentation of the optic disc, can be caused by increased intraocular pressure. Additionally, a pale color of the nerve can suggest damage to the nerve from poor blood flow or increased intraocular pressure. Special cameras can be used to take photographs of the optic nerve to compare changes over time.

Visual field testing : Actually maps the visual fields to detect any early (or late) signs of glaucomatous damage to the optic nerve. In order to find and follow glaucoma, visual fields are measured by a computer one eye at a time. For this procedure, one eye is covered and the patient places his or her chin in a type of bowl. Lights of various intensity and size are projected randomly around the bowl. Then, when the patient sees a light, he or she pushes a button. This

process produces a computerized map of the visual field, outlining the areas where the eye can or cannot see.

Optic nerve tomography and nerve fiber analysis create a three-dimensional image of the optic nerve to evaluate the nerve fiber layer and better evaluate optic nerve damage.

Management

The modern goals of glaucoma management are to avoid glaucomatous damage and nerve damage and preserve visual field and total quality of life for patients, with minimal side effects. This requires appropriate diagnostic techniques and follow-up examinations and judicious selection of treatments for the individual patient. Although intraocular pressure is only one of the major risk factors for glaucoma, lowering it via various pharmacological and/or surgical techniques is currently the mainstay of glaucoma treatment.

Vascular flow and neurodegenerative theories of glaucomatous optic neuropathy have prompted studies on various neuroprotective therapeutic strategies, including nutritional compounds, some of which may be regarded by clinicians as safe for use now, while others are on trial.

Balance and postural control

Because of the important role of the visual system in balance and maintaining posture in human beings, glaucoma patients should consider themselves at greater risk of falls, and would be advised to take the necessary precautions to help prevent any accidents. In addition, since the peripheral visual system has such a high contribution to this intrinsic balancing mechanism, the severity of glaucoma and degree of visual field obstruction should also be considered. Because of the relationship of glaucoma with age, other associated factors affecting balance (i.e. impaired proprioception) may also be present, further increasing the risk of falls. Of interesting note, one cohort of open-angle glaucoma patients had their ability to maintain posture measured (via measurements of sway) in binocular (two-eyed) and monocular (one-eyed, using both affected and unaffected eyes) conditions, as well as with their eyes closed.

These patients had increased sway (worse balance) in their one-eyed conditions compared to the two-eyed conditions and reduced sway (better balance) when using one eye than when their eyes were closed, but there were no significant differences between the two monocular conditions, with the unaffected eye having only slightly (but not significantly) reduced sway than when using their affected eyes. All patients in each condition displayed increased sway compared to their age-matched controls.

Medication

Intraocular pressure can be lowered with medication, usually eye drops. Several different classes of medications are used to treat glaucoma, with several different medications in each class.

Each of these medicines may have local and systemic side-effects. Adherence to medication protocol can be confusing and expensive; if side-effects occur, the patient must be willing either to tolerate them, or to communicate with the treating physician to improve the drug regimen. Initially, glaucoma drops may reasonably be started in either one or in both eyes.

Poor compliance with medications and follow-up visits is a major reason for vision loss in glaucoma patients. A 2003 study of patients found half failed to fill their prescriptions the first time and one-fourth failed to refill their prescriptions a second time. Patient education and communication must be ongoing to sustain successful treatment plans for this lifelong disease with no early symptoms.

The possible neuroprotective effects of various topical and systemic medications are also being investigated.

- ❑ Prostaglandin analogs, such as latanoprost, bimatoprost and travoprost, increase uveoscleral outflow of aqueous humor. Bimatoprost also increases trabecular outflow.
- ❑ Topical beta-adrenergic receptor antagonists, such as timolol, levobunolol and betaxolol, decrease aqueous humor production by the ciliary body.
- ❑ Alpha2-adrenergic agonists, such as brimonidine and apraclonidine, work by a dual mechanism, decreasing aqueous humor production and increasing uveoscleral outflow.
- ❑ Less-selective alpha agonists, such as epinephrine, decrease aqueous humor production through vasoconstriction of ciliary body blood vessels, useful only in open-angle glaucoma. Epinephrine's mydriatic effect, however, renders it unsuitable for closed-angle glaucoma due to further narrowing of the uveoscleral outflow (i.e. further closure of trabecular meshwork, which is responsible for absorption of aqueous humor).
- ❑ Miotic agents (parasympathomimetics), such as pilocarpine, work by contraction of the ciliary muscle, opening the trabecular meshwork and allowing increased outflow of the aqueous humour. Echothiophate, an acetylcholinesterase inhibitor, is used in chronic glaucoma.
- ❑ Carbonic anhydrase inhibitors, such as dorzolamide, brinzolamide and acetazolamide, lower secretion of aqueous humor by inhibiting carbonic anhydrase in the ciliary body.
- ❑ Physostigmine is also used to treat glaucoma.
- ❑ Marijuana was found, in the early 1970s, to reduce pressure in the eyes, though how the cannabinoids in marijuana produce this effect remains unknown.

Surgery

Both laser and conventional surgeries are performed to treat glaucoma. Surgery is the primary therapy for those with congenital glaucoma. Generally, these surgeries are a temporary solution, as there is not yet a cure for glaucoma.

Canaloplasty

Canaloplasty is a nonpenetrating procedure using microcatheter technology. To perform a canaloplasty, an incision is made into the eye to gain access to the Schlemm's canal in a similar fashion to a viscocanalostomy. A microcatheter will circumnavigate the canal around the iris, enlarging the main drainage channel and its smaller collector channels through the injection of a sterile, gel-like material called viscoelastic substance. The catheter is then removed and a suture is placed within the canal and tightened.

By opening the canal, the pressure inside the eye may be relieved, although the reason is unclear, since the canal (of Schlemm) does not have any significant fluid resistance in glaucoma or healthy eyes. Long-term results are not available.

Laser surgery

Argon laser trabeculoplasty (ALT) may be used to treat open-angle glaucoma. It is a temporary solution, not a cure. A 50- m argon laser spot is aimed at the trabecular meshwork to stimulate opening of the mesh to allow more outflow of aqueous fluid.

Usually, half of the angle is treated at a time. Traditional laser trabeculoplasty uses a thermal argon laser in an argon laser trabeculoplasty procedure.

A newer type of laser trabeculoplasty uses a "cold" (nonthermal) laser to stimulate drainage in the trabecular meshwork. This newer procedure, selective laser trabeculoplasty (SLT), uses a 532-nm, frequency-doubled, Q-switched Nd:YAG laser, which selectively targets melanin pigment in the trabecular meshwork cells. Studies show SLT is as effective as ALT at lowering eye pressure. In addition, SLT may be repeated three to four times, whereas ALT can usually be repeated only once.

Nd:YAG laser peripheral iridotomy (LPI) may be used in patients susceptible to or affected by angle closure glaucoma or pigment dispersion syndrome. During laser iridotomy, laser energy is used to make a small, full-thickness opening in the iris to equalize the pressure between the front and back of the iris, thus correcting any abnormal bulging of the iris. In people with narrow angles, this can uncover the trabecular meshwork. In some cases of intermittent or short-term angle closure, this may lower the eye pressure. Laser iridotomy reduces the risk of developing an attack of acute angle closure. In most cases, it also reduces the risk of developing chronic angle closure or of adhesions of the iris to the trabecular meshwork.

Diode laser cycloablation lowers IOP by reducing aqueous secretion by destroying secretory ciliary epithelium.

Trabeculectomy

The most common conventional surgery performed for glaucoma is the trabeculectomy. Here, a partial thickness flap is made in the scleral wall of the eye and a window opening is made under the flap to remove a portion of the trabecular meshwork. The scleral flap is then sutured loosely back in place to allow fluid to flow out of the eye through this opening, resulting in lowered intraocular pressure and the formation of a bleb or fluid bubble on the surface of the eye. Scarring can occur around or over the flap opening, causing it to become less effective or lose effectiveness altogether. Traditionally, chemotherapeutic adjuvants, such as mitomycin C (MMC, 0.5–0.2 mg/ml) or 5-fluorouracil (5-FU, 50 mg/ml), are applied with soaked sponges on the wound bed to prevent filtering blebs from scarring by inhibiting fibroblast proliferation. Contemporary alternatives include the sole or combinative implementation of nonchemotherapeutic adjuvants, such as collagen matrix implant or other biodegradable spacers, to prevent super scarring by randomization and modulation of fibroblast proliferation in addition to the mechanical prevention of wound contraction and adhesion.

Glaucoma drainage implants

Professor Anthony Molteno developed the first glaucoma drainage implant, in Cape Town in 1966. Since then, several different types of implants have followed on from the original, the Baerveldt tube shunt or the valved implants, such as the Ahmed glaucoma valve implant or the ExPress Mini Shunt and the later generation pressure ridge Molteno implants. These are indicated for glaucoma patients not responding to maximal medical therapy, with previous failed guarded filtering surgery (trabeculectomy). The flow tube is inserted into the anterior chamber of the eye and the plate is implanted underneath the conjunctiva to allow flow of aqueous fluid out of the eye into a chamber called a bleb.

- ❑ The first-generation Molteno and other nonvalved implants sometimes require the ligation of the tube until the bleb formed is mildly fibrosed and water-tight. This is done to reduce postoperative hypotony-sudden drops in postoperative intraocular pressure.
- ❑ Valved implants, such as the Ahmed glaucoma valve, attempt to control postoperative hypotony by using a mechanical valve.

The ongoing scarring over the conjunctival dissipation segment of the shunt may become too thick for the aqueous humor to filter through. This may require preventive measures using antifibrotic medications, such as 5-fluorouracil or mitomycin-C (during the procedure) or other nonantifibrotic medication methods, such as collagen matrix implant, or biodegradable spacer or later on create a necessity for revision surgery with the sole or combinative use of donor patch grafts or collagen matrix implant. And for glaucomatous painful blind eye and some cases of glaucoma, cyclocryotherapy for ciliary body ablation could be considered to be performed.

Laser-assisted nonpenetrating deep sclerectomy

Nonpenetrating deep sclerectomy (NPDS) surgery is a modified procedure, in which instead of puncturing the scleral bed and trabecular meshwork under a scleral flap, a second deep scleral flap is created, excised, with further procedures of deroofting the Schlemm's canal, upon which, percolation of liquid from the inner eye is achieved and thus alleviating intraocular pressure, without penetrating the eye. NPDS is demonstrated to cause significantly fewer side effects than trabeculectomy. However, NPDS is performed manually and requires higher level of skills that may be assisted with instruments. In order to prevent wound adhesion after deep scleral excision and to maintain good filtering results, NPDS as with other nonpenetrating procedures is sometimes performed with a variety of biocompatible spacer or devices.

Laser-assisted NPDS is performed with the use of a CO2 laser system. The laser-based system is self-terminating once the required scleral thickness and adequate drainage of the intraocular fluid have been achieved. This self-regulation effect is achieved as the CO2 laser essentially stops ablating as soon as it comes in contact with the intraocular percolated liquid, which occurs as soon as the laser reaches the optimal residual intact layer thickness.

Research

- ❑ The Advanced Glaucoma Intervention Study is a large American

National Eye Institute (NEI)-sponsored study designed "to assess the long-range outcomes of sequences of interventions involving trabeculectomy and argon laser trabeculoplasty in eyes that have failed initial medical treatment for glaucoma". It recommends different treatments based on race.

- ❑ The Early Manifest Glaucoma Trial is another NEI study which found immediate treatment of people who have early-stage glaucoma can delay progression of the disease.
- ❑ The Ocular Hypertension Treatment Study, also an NEI study, found topical ocular hypotensive medication was effective in delaying or preventing onset of primary open-angle glaucoma (POAG) in individuals with elevated intraocular pressure (IOP). Although this does not imply all patients with borderline or elevated IOP should receive medication, clinicians should consider initiating treatment for individuals with ocular hypertension who are at moderate or high risk for developing POAG.
- ❑ The Blue Mountains Eye Study was the first large, population-based assessment of visual impairment and common eye diseases of a representative older Australian community sample. Risk factors for glaucoma and other eye disease were determined.

Prevention

All adults should have a complete eye examination before age of 40 years or sooner if someone have risk factors for glaucoma or other eye problems. People are more likely to get glaucoma if they are African American or have a family history of open angle glaucoma.

Conclusion

New eyedrops will continue to become available for the treatment of glaucoma. Some drops will be new classes of agents. Although lowering intraocular pressure is still the primary method of treating glaucoma, experts see the disease as more a neurological condition than an eye disorder. Animal models have shown that certain chemical mediators can reduce injury or death of nerve cells. Proving such a benefit for the human optic nerve, however, is more difficult because, for one thing, biopsy or tissue specimens are not readily available.

Nevertheless, if any of these mediators in eyedrops can be shown to protect the human optic nerve from glaucomatous damage, this would be a wonderful advance in preventing blindness. Finally, increased efforts to enhance public awareness of glaucoma, national free screenings for those individuals at risk, earlier diagnosis and treatment and better compliance with treatment are our best hopes to reduce vision loss from glaucoma.

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Multiple myeloma (MM) is a debilitating malignancy. First described in 1848, MM is characterized by a proliferation of malignant plasma cells and a subsequent overabundance of monoclonal paraprotein (M protein). An important feature of MM is that the antibody-forming cells (ie, plasma cells) are malignant and therefore, may cause unusual manifestations.

Pathophysiology

Neoplastic plasma cells involve more than 10% of the bone marrow. Increasing evidence suggests that the bone marrow microenvironment of tumor cells plays a pivotal role in the pathogenesis of myelomas. This information has resulted in the expansion of treatment options.

In MM malignant plasma cells and plasmacytoid lymphocytes are the most mature cells of B-lymphocytes. B-cell maturation is associated with a programmed rearrangement of DNA sequences in the process of encoding the structure of mature immunoglobulins. It is characterized by overproduction of monoclonal immunoglobulin G (IgG), immunoglobulin A (IgA) and/or light chains, which may be identified with serum protein electrophoresis or urine protein electrophoresis.

The role of cytokines in the pathogenesis of MM is an important area of research. Interleukin -6 is an important factor promoting the in vitro growth of myeloma cells. Other important cytokines are tumor necrosis factor and IL-1b.

The pathophysiologic basis for the clinical sequelae of MM involves the skeletal, hematologic, renal and nervous systems, as well as general processes.

□ Skeletal processes

Plasma-cell proliferation causes extensive skeletal destruction with osteolytic lesions, anemia, and hypercalcemia. Mechanisms for hypercalcemia include bony involvement and possibly, humoral mechanisms. Isolated plasmacytomas (which affect 2-10% of patients) lead to hypercalcemia through production of the osteoclast-activating factor.

Destruction of bone and its replacement by tumor may lead to pain, spinal cord compression, and pathologic fracture. The mechanism of spinal cord compression symptoms may be the development of an epidural mass with compression, a compression fracture of a vertebral body destroyed by multiple myelom or rarely, an extradural mass.

□ Hematologic processes

Bone marrow infiltration by plasma cells results in neutropenia, anemia, and thrombocytopenia. In terms of bleeding, M protein may interact specifically with clotting factors, leading to defective aggregation of platelets.

□ Renal processes

The most common mechanisms of renal injury in MM are direct tubular injury, amyloidosis, or involvement by plasmacytoma. Renal conditions that may be observed include hypercalcemic nephropathy, hyperuricemia, light-chain nephropathy, amyloidosis and glomerulosclerosis.

□ Neurologic processes

The nervous system may be involved as a result of radiculopathy and/or cord compression due to nerve compression and skeletal destruction.

□ General processes

General pathophysiologic processes include hyperviscosity syndrome. This syndrome is infrequent in MM and occurs with IgG1, IgG3 or IgA. MM may involve sludging in the capillaries, which results in purpura, retinal hemorrhage, papilledema, coronary ischemia or central nervous system (CNS) symptoms (eg, confusion, vertigo, seizure). Cryoglobulinemia causes Raynaud phenomenon, thrombosis and gangrene in the extremities.

Epidemiology

MM accounts for 10% of all hematologic cancers. The age-adjusted annual incidence of MM is 4.3 cases per 100,000 white men, 3 cases per 100,000 white women, 9.6 cases per 100,000 black men and 6.7 cases per 100,000 black women.

The American Cancer Society estimated that in the United States, 20,580 new cases of MM would be diagnosed during 2009, with 11,680 cases occurring in men and 8,900 in women. The lifetime risk of getting MM is 1 in 161 (0.62%).

The median age of patients with MM is 68 years for men and 70 years for women. Only 18% of patients are younger than 50 years, and 3% of patients are younger than 40 years. The male-to-female ratio of multiple myeloma is approximately 3:2.

In the United States, African Americans are twice as likely as whites to have myeloma, with a ratio of 2:1. Myeloma is rare among people of Asian descent, with an incidence of only 1-2 cases per 100,000 population.

According to a study of the ethnic disparities among patients with MM, Hispanics had the youngest median age at diagnosis (65 years) and Whites had the oldest (71 years). Asians had the best overall survival rates, while Hispanics had the worst.

Etiology

The precise etiology of MM has not yet been established. Roles have been suggested for a variety of factors, including genetic causes, environmental or occupational causes, monoclonal gammopathy, radiation, chronic inflammation and infection.

Genetic causes

MM has been reported in 2 or more first-degree relatives and in identical twins, although no evidence suggests a hereditary basis for the disease. A study by the Mayo clinic found MM in 8 siblings from a group of 440 patients; these 8 siblings had different heavy chains but the same light chains.

Some studies have shown that abnormalities of certain oncogenes, such as c-myc, are associated with development of plasma cell tumors. Abnormalities of oncogenes such as N-RAS and K-RAS are associated with bone marrow relapse. Abnormalities of tumor suppressor genes, such as p53, have been shown to be associated with spread to other organs.

Ongoing research is investigating whether human leukocyte antigen (HLA)-Cw5 or HLA-Cw2 may play a role in the pathogenesis of multiple myeloma.

Environmental or occupational causes

Case-controlled studies have suggested a significant risk of developing MM in individuals with significant exposures in the agriculture, food, and petrochemical industries. An increased risk has been reported in farmers, especially in those who use herbicides and insecticides, and in people exposed to benzene and other organic solvents. Long-term (>20 y) exposure to hair dyes has been tied to an excessive risk of developing MM.

Monoclonal gammopathy

Approximately 19% of patients with MG develop MM within 2-19 years. A study by Wadhera et al examined secondary MGUS that developed in patients with MM. Of 1942 patients with MM, 128 (6.6%) developed a secondary MGUS at a median of 12 months from the diagnosis of MM. Overall survival was superior in patients with MM who developed secondary MGUS compared with the rest of the cohort.

Radiation

Radiation may play a role in some patients. An increased risk has been reported in atomic-bomb survivors exposed to more than 50 Gy. In 109,000 survivors of the atomic bombing of Nagasaki during World War II, 29 died from multiple myeloma between 1950 and 1976. Some more recent studies, however, do not confirm that these survivors have an increased risk of developing multiple myeloma.

A recent study of workers at the Oak Ridge Diffusion Plant in eastern Tennessee showed only a weak correlation of risk of multiple myeloma to uranium exposure.

Chronic inflammation

A relationship between MM and preexisting chronic inflammatory diseases has been suggested. However, a case-control study provides no support for the role of chronic antigenic stimulation.

Infection

Human herpesvirus 8 infection of bone marrow dendritic cells was found in patients with MM and in some patients with MGUS.

Presentation

□ History

Presenting symptoms of multiple myeloma (MM) include bone pain, pathologic fractures, weakness, anemia, infection (often pneumococcal), hypercalcemia, spinal cord compression or renal failure. The diagnosis is incidental in 30% of cases. MM is often discovered

through routine blood screening when patients are being evaluated for unrelated problems. Typically, a large gap between the total protein and the albumin levels observed on an automated chemistry panel suggests a problem (protein minus albumin equals globulin).

In one third of patients, MM is diagnosed after a pathologic fracture occurs; such fractures commonly involve the axial skeleton. Two thirds of patients complain of bone pain, commonly with lower back pain. This bone pain is frequently located in the back, long bones, skull, and/or pelvis.

Patients may also complain of nonspecific constitutional symptoms related to hyperviscosity and hypercalcemia.

□ Bone pain

Bone pain is the most common presenting symptom in MM. Most case series report that 70% of patients have bone pain at presentation. The lumbar spine is one of the most common sites of pain.

□ Pathologic fractures and bone lesions

Pathologic fractures are very common in MM; 93% of patients have more than one site of bony involvement. A severe bony event is a common presenting issue.

□ Spinal cord compression

The symptoms that should alert physicians to consider spinal cord compression are back pain, weakness, numbness, or dysesthesias in the extremities. Because spinal cord compressions in MM occur at multiple levels, comprehensive evaluation of the spine is warranted. Patients who are ambulatory at the start of therapy have the best likelihood of preserving function and avoiding paralysis.

□ Bleeding

Occasionally, a patient may come to medical attention for bleeding resulting from thrombocytopenia. Rarely, monoclonal protein may absorb clotting factors and lead to bleeding.

□ Hypercalcemia

Confusion, somnolence, bone pain, constipation, nausea, and thirst are the presenting symptoms of hypercalcemia. This complication may be present in as many as 30% of patients with MM at presentation. In most solid malignancies, hypercalcemia carries an ominous prognosis, but in MM, its occurrence does not adversely affect survival.

□ Infection

Abnormal humoral immunity and leukopenia may lead to infection. Pneumococcal organisms are commonly involved, but shingles (ie, herpes zoster) and *Haemophilus* infections are also more common among patients with MM.

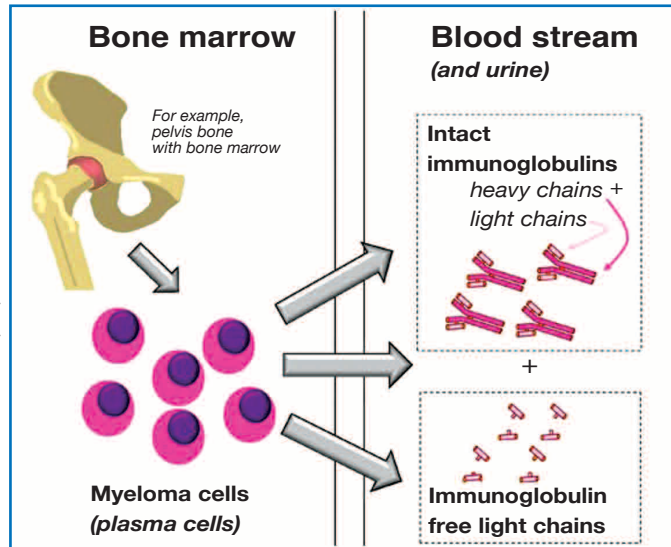


Figure : Myeloma cells

□ Hyperviscosity

Hyperviscosity may be associated with a number of symptoms, including, generalized malaise, infection, fever, paresthesia, sluggish mentation, and sensory loss. Patients may report headaches and somnolence, and they may bruise easily and have hazy vision. Patients with MM typically experience these symptoms when their serum viscosity is greater than 4 times that of normal serum.

Epistaxis may be a presenting symptom of MM with a high tumor volume. Occasionally, patients may have such a high volume of monoclonal protein that their blood viscosity increases, resulting in complications such as stroke, myocardial ischemia, or infarction.

□ Neurologic symptoms

Carpal tunnel syndrome is a common complication of myeloma. Meningitis (especially that resulting from pneumococcal or meningococcal infection) is more common in patients with MM. Some peripheral neuropathies have been attributed to MM. Long-term neurologic function is directly related to the rapidity of the diagnosis and the institution of appropriate therapy for MM.

□ Anemia

Anemia, which may be quite severe, is the most common cause of weakness in patients with MM.

Physical Examination

On general examination, the eyes may show exudative macular detachment, retinal hemorrhage, or cotton-wool spots. Pallor from anemia may be present. Ecchymoses or purpura from thrombocytopenia may be evident.

Bony tenderness is not uncommon in MM, resulting from focal lytic destructive bone lesions or pathologic fracture. Pain without tenderness is typical. Pathologic fractures may be observed. The risk of fracture is lower in upper extremity lesions than in lower-extremity lesions. Even a small cortical defect can decrease torsional strength by as much as 60% (stress riser effect).

Neurologic findings may include a sensory level change, neuropathy, myopathy, a Tinel sign or a Phalen sign due to carpal tunnel compression secondary to amyloid deposition.

Extramedullary plasmacytomas, which consist of soft-tissue masses of plasma cells, are not uncommon. Plasmacytomas have been described in almost every site in the body. Although the aerodigestive tract is the most common location, reports also describe orbital, ear canal, cutaneous, gastric, rectal, prostatic, and retroperitoneal lesions.

On evaluation of the abdomen, hepatosplenomegaly may be discovered. Cardiovascular system examination may reveal cardiomegaly secondary to immunoglobulin deposition.

Amyloidosis may develop in some patients with MM. The characteristic physical examination findings that suggest amyloidosis include the following :

- Shoulder pad sign
- Macroglossia
- Typical skin lesions

□ Postprotoscopic peripalpebral purpura

The shoulder pad sign is defined by bilateral swelling of the shoulder joints secondary to amyloid deposition. The swelling feels as hard and rubbery. Amyloidosis may also be associated with carpal tunnel syndrome and subcutaneous nodules.

Macroglossia may occur secondary to amyloid deposition in the tongue and is a common finding in patients with amyloidosis.

Skin lesions that have been described as waxy papules or nodules may occur on the torso, ears, or lips.

Postprotoscopic peripalpebral purpura strongly suggests amyloidosis. Patients may develop raccoonlike dark circles around their eyes following any procedure that parallels a prolonged Valsalva maneuver. The capillary fragility associated with amyloidosis may account for this observation. In the past, this correlation was observed when patients underwent rectal biopsies to make the diagnosis.

Diagnostic Considerations

The most widely accepted schema for the diagnosis of multiple myeloma (MM) uses particular combinations of laboratory, imaging, and procedure findings as diagnostic criteria. The findings are as follows :

- I = Plasmacytoma on tissue biopsy
- II = Bone marrow with greater than 30% plasma cells
- III = Monoclonal globulin spike on serum protein electrophoresis, with an immunoglobulin (Ig) G peak of greater than 3.5 g/dL or an IgA peak of greater than 2 g/dL, or urine protein electrophoresis (in the presence of amyloidosis) result of greater than 1 g/24 h
- a = Bone marrow with 10-30% plasma cells
- b = Monoclonal globulin spike present but less than category III
- c = Lytic bone lesions
- d = Residual IgM level less than 50 mg/dL, IgA level less than 100 mg/dL, or IgG level less than 600 mg/dL

The following combinations of findings are used to make the diagnosis of multiple myeloma :

- I plus b, c or d
- II plus b, c or d
- III plus a, c or d
- a plus b plus c
- a plus b plus d

Indolent MM is a subset of the disease in which patients have no (or very limited) bone disease, a performance status greater than 70%, a hemoglobin level greater than 10 g/dL, a calcium level within the reference range, a creatinine level less than 2 mg/dL, no infections, and low (< 7 g/dL for IgG, < 5 g/dL for IgA) M protein levels.

Smoldering MM is the same as indolent MM, except that these patients have less than 30% plasma cells in their bone marrow, and they have no bone disease.

Approach Considerations

The risk of renal failure should be considered, especially in the setting of contrast medium injection for imaging studies. Take care to limit patients' exposure and maintain hydration.

The 2009 International Myeloma Workshop developed guidelines for standard investigative workup in patients suspected to have multiple myeloma. These guidelines included the following :

- ❑ Serum and urine assessment for monoclonal protein (densitometer tracing and nephelometric quantitation; immunofixation for confirmation)
- ❑ Serum-free light chain assay (in all patients with newly diagnosed plasma cell dyscrasias)
- ❑ Bone marrow aspiration and/or biopsy
- ❑ Serum beta(2)-microglobulin, albumin, and lactate dehydrogenase measurement
- ❑ Standard metaphase cytogenetics
- ❑ Fluorescent in situ hybridization
- ❑ Skeletal survey
- ❑ MRI
- ❑ **Complete Blood Count**

A complete blood count (CBC) should be performed to determine if the patient has anemia, thrombocytopenia, or leukopenia. The CBC and differential may show pancytopenia, abnormal coagulation, and an increased erythrocyte sedimentation rate (ESR). The reticulocyte count is typically low. Peripheral blood smears may show Rouleau formation.

❑ Metabolic Panel

A comprehensive metabolic panel should be obtained to assess levels of total protein, albumin and globulin, blood urea nitrogen (BUN), creatinine, and uric acid (uric acid will be high if the patient has high cell turnover or is dehydrated).

❑ Urine Collection

A 24-hour urine sample should be collected for quantification of the Bence Jones protein (ie, lambda light chains), protein, and creatinine clearance. Quantification of proteinuria is useful for the diagnosis of MM (>1 g of protein in 24 h is a major criterion) and for monitoring the response to therapy. Creatinine clearance can be useful for defining the severity of the patient's renal impairment.

❑ Electrophoresis and Immunofixation

Serum protein electrophoresis (SPEP) is used to determine the type of each protein present and may indicate a characteristic curve (where the spike is observed). Urine protein electrophoresis (UPEP) is used to identify the presence of the Bence Jones protein in urine. Immunofixation is used to identify the subtype of protein (ie, IgA lambda).

The 2011 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on Oncology, Multiple Myeloma

Version recommend the use of serum free light chain assay as well as fluorescence in situ hybridization (FISH) for 1q21 amplification as part of the initial diagnostic workup.

Chemical screening, including calcium and creatinine may show azotemia, hypercalcemia, an elevated alkaline phosphatase level, and hypoalbuminemia. A high lactate dehydrogenase (LDH) level is predictive of an aggressive lymphomalike course.

SPEP is a useful screening test for detecting M proteins. An M component is usually detected by means of high-resolution SPEP. The kappa-to-lambda ratio has been recommended as a screening tool for detecting M-component abnormalities. An M-component serum concentration of 30 g/L is a minimal diagnostic criterion for MM. In about 25% of patients, M protein cannot be detected by using SPEP.

Routine urinalysis may not indicate the presence of Bence Jones proteinuria. Therefore, a 24-hour urinalysis by means of UPEP or immunoelectrophoresis may be required. UPEP or immunoelectrophoresis can also be used to detect an M component and kappa or lambda light chains. The most important means of detecting MM is electrophoretic measurement of immunoglobulins in both serum and urine.

❑ Quantitative Immunoglobulin Levels (IgG, IgA, IgM)

Suppression of nonmyelomatous immunoglobulin is a minor diagnostic criterion for MM. The level of MM protein (M protein level), as documented by the immunoglobulin level, can be useful as a marker to assess the response to therapy.

❑ Beta-2 Microglobulin

Beta-2 microglobulin is a surrogate marker for the overall body tumor burden. The level of beta-2 microglobulin is increased in patients with renal insufficiency without MM, which is one reason that it is a useful prognostic factor in MM. The prognosis of patients with MM and impaired renal function is reduced.

❑ C-Reactive Protein

C-reactive protein (CRP) is a surrogate marker of interleukin-6 activity. IL-6 is often referred to as the plasma cell growth factor. Like beta-2 microglobulin, CRP is useful for prognosis.

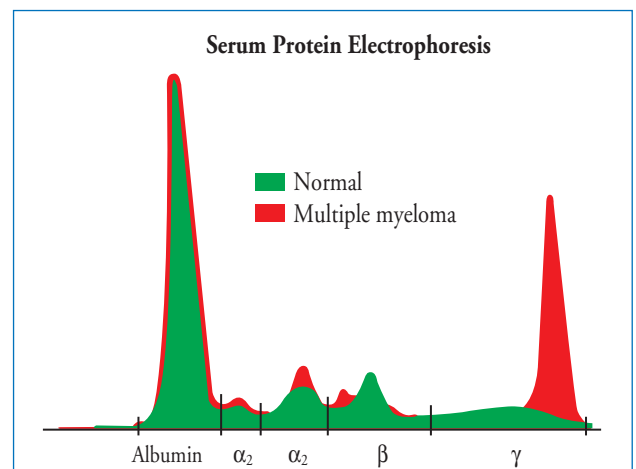


Figure : Serum Protein Electrophoresis

□ Serum Viscosity

The serum viscosity should be checked in patients with central nervous system (CNS) symptoms, nosebleeds, or very high M protein levels.

□ Radiography

Simple radiography is indicated for the evaluation of skeleton lesions, and a skeletal survey is performed when myeloma is in the differential diagnosis. Plain radiography remains the gold standard imaging procedure for staging newly diagnosed and relapsed myeloma patients, according to an International Myeloma Working Group consensus statement.

A complete skeletal series at diagnosis of MM, including the skull, the long bones (to look for impending fractures), and the spine should be taken.

Conventional plain radiography can usually depict lytic lesions. Such lesions appear as multiple, rounded, punched-out areas found in the skull, vertebral column, ribs, and/or pelvis. Less common but not rare sites of involvement include the long bones. Plain radiographs can be supplemented by computed tomography (CT) scanning to assess cortical involvement and risk of fracture. Diffuse osteopenia may suggest myelomatous involvement before discrete lytic lesions are apparent.

□ Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is useful in detecting thoracic and lumbar spine lesions, paraspinal involvement, and early cord compression. Findings from MRI of the vertebrae are often positive when plain radiographs are not. MRI can depict as many as 40% of spinal abnormalities in patients with asymptomatic gammopathies in whom radiographic studies are normal. For this reason, evaluation of symptomatic patients with MRI to obtain a clear view of the spinal column and to assess the integrity of the spinal cord is important.

□ Positron Emission Tomography

Comparative studies have suggested the possible utility of positron emission tomography (PET) scanning in the evaluation of MM. For example, a comparison study of PET scanning and whole-body MRI in patients with bone marrow biopsy-proven multiple myeloma found that although MRI had higher sensitivity and specificity than PET in the assessment of disease activity, when used in combination and with concordant findings, the 2 modalities had a specificity and positive predictive value of 100%. However, PET scanning has not yet been integrated into standard practice. A study by Zamagni et al found that 18 fluorodeoxyglucose (FDG) PET/CT scan findings were reliable predictors of prognosis among patients with multiple myeloma who had undergone thalidomide-dexamethasone induction therapy and double autotransplantation

□ Bone Scan

Bone scans should not be used to evaluate MM. Cytokines secreted by MM cells suppress osteoblast activity; therefore, typically, no increased uptake is observed. On technetium bone scanning, more than 50% of lesions can be missed.

□ Aspiration and Biopsy

MM is characterized by an increased number of bone marrow plasma cells. Plasma cells show low proliferative activity, as measured by using the labeling index. This index is a reliable parameter for the diagnosis of MM. High values are strongly correlated with progression of the disease. Bone marrow biopsy enables a more accurate evaluation of malignancies than does bone marrow aspiration.

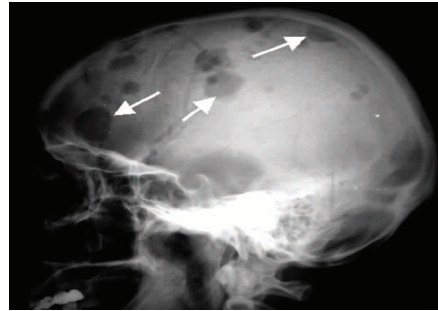


Figure : X-ray skull showing lytic bone lesions

□ Histologic Findings

Plasma cells are 2-3 times larger than typical lymphocytes; they have eccentric nuclei that are smooth (round or oval) in contour with clumped chromatin and have a perinuclear halo or pale zone. The cytoplasm is basophilic. Many MM cells have characteristic, but not diagnostic, cytoplasmic inclusions, usually containing immunoglobulin. The variants include Mott cells, Russell bodies, grape cells, and morula cells. Bone marrow examination reveals plasma cell infiltration, often in sheets or clumps. This infiltration is different from the lymphoplasmacytic infiltration observed in patients with Waldenstrom macroglobulinemia. Analysis of bone biopsy specimens may reveal plasmacytic, mixed cellular, or plasmablastic histologic findings. With the plasmacytic type, median survival is approximately 39.7 months. With the mixed cellular type, survival is 16.1 months and with the plasmablastic type, survival is 9.8 months.

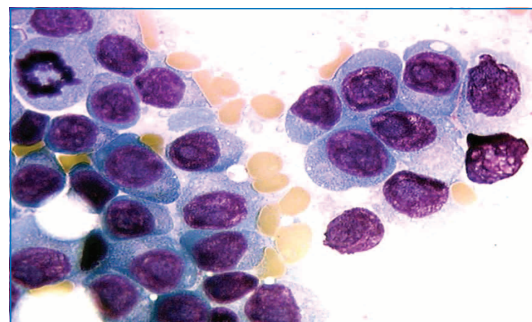


Figure : Malignant plasma cells

□ Cytogenetic Analysis

Cytogenetic analysis of the bone marrow may contribute significant prognostic information in multiple myeloma. The most significant cytogenetic abnormality appears to be deletion of 17p13. This abnormality is associated with shorter survival, more extramedullary disease, and hypercalcemia. This locus is the site of the p53 tumor suppressor gene. Chromosome 1 abnormalities and c-myc defects are also significant prognostic factors in multiple myeloma.

Although not as well defined as in other hematologic malignancies, such as acute leukemia, risk-adapted therapy based on cytogenetic abnormalities is at the forefront of myeloma research.

Staging

Staging is a cumulative evaluation of all of the diagnostic information garnered and is a useful tool for stratifying the severity of patients' disease. Currently, 2 staging systems for multiple myeloma are in use: the Salmon-Durie system, which has been widely used since 1975; and the International Staging System, developed by the International Myeloma Working Group and introduced in 2005.

Salmon-Durie staging system

The Salmon-Durie classification of MM is based on 3 stages and additional subclassifications.

In stage I, the MM cell mass is less than 0.6×10^{12} cells/m² and all of the following are present:

- ❑ Hemoglobin value greater than 10 g/dL
- ❑ Serum calcium value less than 12 mg/dL (normal)
- ❑ Normal bone structure (scale 0) or only a solitary bone plasmacytoma on radiographs
- ❑ Low M-component production rates (IgG value less than 5 g/dL, IgA value less than 3 g/dL, urine light-chain M component on electrophoresis less than 4 g/24 h)

In stage II, the MM cell mass is $0.6-1.2 \times 10^{12}$ cells/m². The other values fit neither those of stage I nor those of stage III.

In stage III, the MM cell mass is greater than 1.2×10^{12} cells/m², and all of the following are present:

- ❑ Hemoglobin value equal to 8.5 g/dL
- ❑ Serum calcium value greater than 12 mg/dL
- ❑ Advanced lytic bone lesions (scale 3) on radiographs
- ❑ High M-component production rates (IgG value greater than 7 g/dL, IgA value greater than 5 g/dL, urine light-chain M component on electrophoresis greater than 12 g/24 h)

Subclassification A includes relatively normal renal function (serum creatinine value < 2 mg/dL), whereas subclassification B includes abnormal renal function (serum creatinine value > 2 mg/dL)

Median survival is as follows:

- ❑ Stage I, > 60 months
- ❑ Stage II, 41 months
- ❑ Stage III, 23 months

Disease in subclassification B has a significantly worse outcome (eg, 2-12 mo survival in 4 separate series).

International Staging System

The International Staging System of the International Myeloma Working Group is also based on 3 stages.

Stage I consists of the following:

- ❑ Beta-2 microglobulin less than or equal to 3.5 g/dL and albumin 3.5 g/dL

- ❑ CRP 4.0 mg/dL
- ❑ Plasma cell labeling index < 1%
- ❑ Absence of chromosome 13 deletion
- ❑ Low serum IL-6 receptor
- ❑ Long duration of initial plateau phase

Stage II consists of the following:

- ❑ Beta-2 microglobulin level 3.5 to < 5.5 g/dL, or
- ❑ Beta-2 microglobulin < 3.5 g/dL and albumin < 3.5 g/dL

Stage III consists of the following:

- ❑ Beta-2 microglobulin of 5.5 g/dL or more

Median survival is as follows:

- ❑ Stage I, 62 months
- ❑ Stage II, 44 months
- ❑ Stage III, 29 months

Complications

Renal failure and insufficiency are seen in 25% of patients with MM, including the following manifestations :

- ❑ Myeloma kidney syndrome with multiple etiologies
- ❑ Amyloidosis with light chains
- ❑ Nephrocalcinosis due to hypercalcemia

Anemia, neutropenia, or thrombocytopenia is due to bone marrow infiltration of plasma cells. Thrombosis and Raynaud phenomenon due to cryoglobulinemia may be present.

Bone disease may result in the following :

- ❑ Severe bone pain, pathologic fracture due to lytic lesions. Lytic disease or fracture may be observed on plain radiographs.
- ❑ Increased bone resorption leading to hypercalcemia
- ❑ Spinal cord compression: This is one of the most severe adverse effects of MM. Reports indicate that as many as 20% of patients develop spinal cord compression at some point during the course of their disease. Symptoms typically include back pain, weakness or paralysis in the legs, numbness, or dysesthesias in the lower extremities. However, depending on the level of involvement, patients may present with upper extremity symptoms.

Radiculopathy and/or cord compression may occur because of skeletal destruction and nerve compression.

Bacterial infection may develop; it is the leading cause of death in patients with myeloma. The highest risk is in the first 2-3 months of chemotherapy.

Purpura, retinal hemorrhage, papilledema, coronary ischemia, seizures, and confusion may occur as a result of hyperviscosity syndrome.

Hypercalcemia may cause polyuria and polydipsia, muscle cramps, constipation, and a change in the patient's mental status.

Treatment

Physicians must understand both the natural history of multiple myeloma (MM) and the limitations of current therapy in the treatment of the disease.

Practice guidelines

In May 2013, the International Myeloma Working Group released practice guidelines for the management of MM-related bone disease. The recommendations, which were based on a review of the literature through August 2012 and a consensus of an interdisciplinary panel of experts, include the following:

- ❑ Consideration of bisphosphonates in all patients with MM receiving first-line antimyeloma therapy, regardless of presence of osteolytic bone lesions on conventional radiography
- ❑ Intravenous (IV) zoledronic acid or pamidronate for preventing skeletal-related events in patients with MM
- ❑ Because of its potential antimyeloma effects and survival benefits, zoledronic acid is preferred in newly diagnosed patients with MM
- ❑ Bisphosphonates should be administered IV every 3 to 4 weeks during initial therapy, but preventive strategies must be instituted to avoid renal toxicity or osteonecrosis of the jaw
- ❑ Zoledronic acid or pamidronate should be continued in patients with active disease and should be resumed after disease relapse
- ❑ Kyphoplasty should be considered for symptomatic vertebral compression fractures
- ❑ Orthopedic consultation should be sought for long bone fractures, spinal cord compression and vertebral column instability
- ❑ Low-dose radiation therapy can be used for palliation of uncontrolled pain, impending pathologic fracture or spinal cord compression

Progression of disease and timing of treatment

An important study evaluated the risk of disease progression in asymptomatic subjects with MM. The study evaluated 638 consecutive untreated subjects with MM. Of these subjects, 95 were asymptomatic and were not treated until their M protein value rose to greater than 5 g/dL. These subjects developed increased bone disease or symptoms of bone disease.



The individuals in this group were designated as either low risk (no bone disease, M protein level < 3 g/dL or Bence Jones protein level < 5 g/24 h) or high risk (lytic bone disease and serum M protein level >3 g/dL or Bence Jones protein level >5 g/24 h).

Intermediate-risk subjects did not have bone disease or an M protein level greater than 3 g/dL or a Bence Jones protein level greater than 5 g/24 h. The patients were evaluated every 2 months.

The median time for disease progression was 10 months in the high-risk group, 25 months in the intermediate-risk group, and 61 months in the low-risk group. At the time of progression, subjects were treated with standard chemotherapy. Their response rates did not significantly differ from those of unselected populations. Median survival time from the institution of chemotherapy did not differ among the groups. Thus, asymptomatic subjects did not benefit from early treatment and delayed treatment did not affect treatment efficacy (survival).

A systematic review also demonstrated a reduction in vertebral compressions and time to progression with early systemic treatment for asymptomatic patients, but this study also revealed an increase in acute leukemia in the early treatment group. The failure to demonstrate improved survival may be due to the small number of patients studied.

The 2011 NCCN Guidelines for MM determined that the term “progression to stage II or higher disease” should be replaced by the term “progression to symptomatic disease”. The 2009 International Myeloma Workshop concluded that detection of any cytogenetic abnormality suggests higher-risk disease, including chromosomal 13 or 13q deletion, t(4;14) and del17p and fluorescence in situ hybridization detection of t(4;14), t(14;16) and del17p. Fluorescence in situ hybridization detection of 13q deletion alone is not considered a high-risk feature. International Staging System stages II and III and high serum beta 2-microglobulin levels are suggestive of higher risk disease.

Current therapeutic approaches

Overall, the care of patients with MM is complex and should focus on treatment of the disease process and any associated complications. Although MM remains incurable, several drug therapies are valuable in the treatment of patients with MM, as are autologous stem cell transplantation, radiation, and surgical care in certain cases.

Patients with MM for whom therapy is indicated typically receive chemotherapy. Understanding of the cell biology of MM and the ability to identify prognostic factors has led to the increasing individualization of treatment for affected patients. Physicians treat many patients with high-dose therapy and peripheral blood or bone marrow stem cell transplantation. A randomized prospective study showed that this approach results in higher response rates and better disease-free survival rates.

The 2011 NCCN MM guidelines added the following therapies :

- ❑ The combination of bortezomib/cyclophosphamide/dexamethasone as primary induction therapy for transplant candidates
- ❑ The combination of bortezomib/dexamethasone (without cyclophosphamide) as primary induction therapy for patients who are not candidates for transplantation
- ❑ The combination of melphalan/prednisone/lenalidomide for primary induction therapy for nontransplant candidates

The resistance mechanisms to chemotherapy in MM are reduced drug concentration at the target site of action, alterations in the drug target, and inhibition of drug-induced apoptosis. Factors mediating myeloma cell growth, patient survival rates, and the complex interaction of MM cells with the bone marrow microenvironment have provided a framework for the rational design of therapeutic agents that may ultimately lead to improved disease-free survival and, potentially, a cure.

A study found that the combination of lenalidomide, bortezomib, pegylated liposomal doxorubicin, and dexamethasone (RVDD) was generally well tolerated and highly active in newly diagnosed patients with multiple myeloma.

Another study determined that aspirin and low-dose warfarin had similar efficacy in reducing serious thromboembolic events, acute cardiovascular events, and sudden deaths in patients with myeloma receiving thalidomide-based regimens compared with low-molecular weight heparin, except in elderly patients.

As monotherapy or in combination, interferon alfa-2b and prednisone modestly prolong the disease-free interval.

A phase 3 randomized, open-label trial of 119 patients with high-risk smoldering MM found that early treatment with lenalidomide plus dexamethasone, followed by maintenance therapy with lenalidomide, delayed progression to symptomatic disease and increased overall survival.

Adjunctive therapy for MM includes radiation therapy to target areas of pain, impending pathologic fracture or existing pathologic fracture. Bisphosphonate therapy serves as prophylaxis (primary, secondary) against skeletal events (eg, hypercalcemia, spinal cord compression, pathologic fracture, need for surgery, need for radiation). Early evidence suggests that it may be effective in treating bone pain and in decreasing the likelihood of lesion recurrence.

Adjunctive therapy may also include erythropoietin, corticosteroids, surgical intervention, or plasmapheresis, as appropriate.

Chemotherapy and Immunosuppression

In patients with symptomatic MM, chemotherapy is required. In asymptomatic patients with MM, treatment is delayed until disease clinically progresses or until serum or urine levels of M protein substantially increase.

The M-component level in serum and/or urine is an indicator of the tumor burden; its reduction after chemotherapy is used as a sign of response. A 50% reduction in M-component is considered a good clinical response (according to the Chronic Leukemia-Myeloma Task Force). Disappearance of the M component on electrophoresis occurs in only 3% of patients, and cure is extraordinarily rare.

Treatment for MM is best categorized on the basis of the patient's age and prognostic factors. 3 separate categories of patients are : (1) young, newly diagnosed patients who are potential transplant candidates; (2) high-risk patients who are potential transplant candidates; and (3) newly diagnosed elderly patients who are not transplant candidates.

Transplantation

Using the patient's own (autologous) bone marrow or peripheral blood stem cells facilitates more intense therapy for MM. After harvesting the stem cells from the patient, physicians can use otherwise lethal doses of total body irradiation and chemotherapy and then "rescue" the patient by reinfusing the harvested cells. This process of myeloablative therapy, followed by the reinfusion of stem cells, is termed autologous stem cell transplantation.

This sequence of therapy allows physicians to use melphalan at an approximately 10-20 times higher dose than is used in standard therapy. In autologous transplantation, the reinfused stem cells or bone marrow act as a support to the patient but do not offer additional anticancer effects.

Tandem autologous transplantation has been proposed as a way of overcoming the incomplete response to a single transplant. A 2-arm trial of single versus tandem transplantation revealed no difference in overall survival at 54 months.

Another 2-arm study that compared single versus tandem transplants for newly diagnosed MM showed that whereas double autologous stem cell transplantation effected superior complete or near-complete response rates, relapse-free survival and event-free survival (EFS), it failed to significantly prolong overall survival. Benefits offered by double autologous stem cell transplantation were particularly evident among patients who failed to achieve at least a near-complete response after one autotransplantation.

A review of long-term outcomes of several autotransplantation trials for MM found that tandem transplantations were superior to both single transplantations and standard therapies and that tandem transplantations with thalidomide were superior to trials without thalidomide. However, postrelapse survival (PRS) was superior when initial EFS exceeded 1280 days and when tandem transplantations had been administered, whereas PRS was shorter when EFS lasted 803 days or less and when trials had included thalidomide and bortezomib.

Two randomized prospective studies compared standard chemotherapy with high-dose autologous transplantation. In the first study of 200 subjects, researchers observed better response rates (81% for the transplantation group vs 57% for the conventionally treated group) and better 5-year event-free survival rates (28% vs 10%). The second study also showed a significant improvement in event-free survival rates and superior quality of life for subjects treated with the high-dose approach.

In highly selected patients with MM, bone marrow allogeneic transplantation is sometimes considered. In this approach, often myeloablative therapy and stem cells (peripheral blood or bone marrow) obtained from a donor, preferably a human leukocyte antigen (HLA)-identical sibling are infused.

The advantage of this approach over autologous transplantation is that the patient is not at risk of being reinfused with MM cells. In addition, the donor's immune system may fight the recipient's cancer (graft vs myeloma effect). Unfortunately, the donor's immune system may also attack the recipient's body (graft vs host effect).

In MM patients with progressive or relapsing disease following autologous stem-cell transplantation, treatment with the combination of bortezomib, thalidomide and dexamethasone is more effective than treatment with thalidomide and dexamethasone alone, although triple therapy is associated with a greater risk of grade 3 neurotoxicity.

Prophylactic Platelet Transfusion

The results of the Trial of Prophylactic Platelets (TOPPS) showed the benefit of prophylactic platelet transfusions for reducing rates of clinically significant bleeding events in patients with hematologic cancers. In this study of 600 blood cancer patients, 301 were randomly assigned to the no-prophylaxis group and 299 to the group that received prophylactic platelet transfusions.

The proportion of patients who had bleeding events of World Health Organization (WHO) grade 2, 3 or 4 was reduced by 7% in the group that received prophylactic platelet transfusions, as compared with the group that did not. Bleeding of WHO grade 2, 3 or 4 occurred in 151 of 300 patients in the no-prophylaxis group and in 128 of 299 in the prophylaxis group (50% vs 43%; adjusted difference in proportions, 8.4 percentage points; 90% confidence interval [CI], 1.7-15.2; $P = .06$ for noninferiority).

Interferon Alfa Therapy

Intense research has focused on the use of interferon alfa to treat MM. This drug does not appear to be effective for inducing remission, and a randomized controlled trial showed that patients do not benefit from the addition of interferon to melphalan and prednisone. Interferon alfa does appear to prolong remission in selected patients with MM. For this use, it may be administered after conventional chemotherapy or bone marrow (stem cell) transplantation has been completed.

The toxicity of interferon and the availability of alternate interventions have significantly limited the role of interferon alfa.

Radiation Therapy

MM is extremely sensitive to radiation. Radiation is used to treat symptomatic lesions and to stabilize bones at risk for fracture. It is also used to treat spinal cord compression. Low-dose, double-hemibody irradiation has been studied as systemic therapy for refractory or relapsed MM, but without dramatic success.

If the pain is mild and if less than 50% of the bone is involved, a course of irradiation can be initiated. Radiation treatment can result in additional early bone loss due to inflammation and weight bearing should be limited for the first 4-6 weeks.

Bisphosphonate Therapy

Bisphosphonates are specific inhibitors of osteoclastic activity and are used to treat bone resorption. They also have a role in the secondary prevention of bony complications in MM, including hypercalcemia, pathologic fracture, and spinal cord compression. Intravenous (IV) pamidronate has been shown to be effective in preventing skeletal complications; zoledronic acid may be significantly more potent than pamidronate.

A randomized placebo-controlled trial of pamidronate in subjects

with MM who had experienced one skeletal event demonstrated that the medication reduced the likelihood of a second skeletal event from 41% to 24% after 9 months of therapy. The investigators also noted improvements in pain, narcotic usage, and quality of life scores.

The American Society of Clinical Oncology (ASCO) recommends IV pamidronate, 90 mg delivered over at least 2 hours, or zoledronic acid, 4 mg delivered over at least 15 minutes every 3-4 weeks. Because the risk for osteonecrosis of the jaw is 9.5-fold greater with zoledronic acid than with pamidronate, patients may prefer pamidronate.

Zoledronic acid doses should be reduced in patients with preexisting mild to moderate renal impairment (estimated creatinine clearance, 30-60 mL/min); the drug is not recommended for use in patients with severe renal impairment. All patients receiving pamidronate or zoledronic acid therapy should be screened every 3-6 months for albuminuria. If unexplained albuminuria (>500 mg/24 hours) is found, ASCO recommends discontinuation of the drug until the renal problems resolve.

Adjunctive Therapy for Complications

According to the 2011 NCCN MM guidelines, novel drugs such as bortezomib can be used with dexamethasone as primary treatment for amyloidosis. The combination of cyclophosphamide/thalidomide/dexamethasone is also recommended for the primary treatment of amyloidosis.

Treatment for myeloma-induced hypercalcemia is the same as that for other malignancy-associated hypercalcemia; however, the dismal outcome observed with hypercalcemia in solid tumors is not observed in MM.

To treat pathologic fractures, physicians should orthopedically stabilize and irradiate these lesions. Careful attention to a patient's bony symptoms, intermittent radiographic surveys, and the use of bisphosphonates may be useful to prevent fractures.

Spinal cord compression is one of the most severe adverse effects of MM. The dysfunction may be reversible, depending on the duration of the cord compression; however, once established, the dysfunction is only rarely fully reversed. Patients who may have spinal cord compression need a rapid evaluation, which may necessitate urgent transfer to a center equipped with MRI for diagnosis or a center with a radiation oncologist for urgent therapy.

Patients with spinal cord compression due to MM should begin corticosteroid therapy immediately to reduce swelling. Urgent arrangements must be made for radiation therapy in order to restore or stabilize neurologic function. Surgery may be indicated.

Erythropoietin may ameliorate anemia resulting from either MM alone or from chemotherapy and has been shown to improve quality of life. A systematic review failed to demonstrate a survival advantage for the use of erythropoietin agents in the treatment of patients with cancer-related anemia.

Acute renal impairment related to MM is typically managed with plasmapheresis to rapidly lower circulating abnormal proteins. Data about this approach are limited, but a small randomized study showed a survival advantage with the use of apheresis.

Hydration (to maintain a urine output of >3 L/d), management of hypercalcemia, and avoidance of nephrotoxins (eg, intravenous contrast media, antibiotics) are also key factors. Conventional therapy may take weeks to months to show a benefit.

Renal impairment resulting from MM is associated with a very poor prognosis. A recent case series demonstrated that patients with renal failure from myeloma may benefit from autologous stem cell transplants, and as many as one third may demonstrate improvement in their renal function with this approach. A report by Ludwig et al suggests that bortezomib-based therapy may restore renal function in MM patients with renal failure.

Surgical Care

Surgical therapy for MM is limited to adjunctive therapy. It consists of prophylactic fixation of pending fractures, decompression of the spinal cord when indicated, and treatment of pathologic fractures.

Prophylactic treatment of impending fractures and the treatment of pathologic fractures may involve bracing. In general, bracing is not effective for the long bones, though it may be effective for treating spinal involvement without neurologic compromise.

Intramedullary fixation is the procedure of choice when surgery is necessary. If the metaphysis or joint surface is involved, resection of the diseased bone and reconstruction with a total joint or, more typically, a hemiarthroplasty is indicated. Modular implants may be required.

Severe destruction of the diaphysis may require reconstruction with combinations of methylmethacrylate, intramedullary nails, or resection and prosthetic replacement.

Although surgical decompression of the spinal cord is sometimes appropriate, posterior laminectomy in this population has been reported to have a mortality rate of 6-10% and it is not superior to radiation. This surgical approach is probably best reserved for cases of MM in which radiation fails. Newer surgical interventions, such as kyphoplasty, in which cement is injected into compressed vertebrae, have been shown to improve function with few complications, although the studies reported have been small.

Dietary Measures

Patients with MM who are receiving bisphosphonate therapy should include adequate calcium in their diet. The dietary supplement of curcumin may slow the progression of smoldering multiple myeloma.

Physical Activity

Patients with MM should be encouraged to be physically active to the extent appropriate for their individual bone status. Physical activity may help maintain bone strength.

In general, patients with activity-related pain in either the femur or the tibia should be given a walker or crutches until a radiographic work up has been completed. Radiation therapy elicits an inflammatory response, and for the first 6 weeks or so, bony resorption may actually weaken the target bone. Given that prophylactic treatment of an impending fracture is usually easier than reconstruction of a pathologic fracture, one should have a low threshold for initiating protected weight bearing.

Prevention of Multiple Myeloma

No preventive measures for MM are known. A study by Chang et al found that routine residential UV radiation exposure may have a protective effect against lymphomagenesis through mechanisms that may be independent of vitamin D.

Prognosis

MM is a heterogeneous disease, with survival ranging from 1 year to more than 10 years. Median survival in unselected patients with MM is 3 years. The 5-year relative survival rate is around 35%. Survival is higher in younger people and lower in the elderly.

The tumor burden and the proliferation rate are the 2 key indicators for the prognosis in patients with MM. Many schemas have been published to aid in determining the prognosis. One schema uses C-reactive protein (CRP) and beta-2 microglobulin (which is an expression of tumor burden) to predict survival as follows :

- ❑ If levels of both proteins are less than 6 mg/L, the median survival is 54 months.
- ❑ If the level of only one component is less than 6 mg/L, the median survival is 27 months.
- ❑ If levels of both protein values are greater than 6 mg/L, the median survival is 6 months.

Poor prognostic factors include the following:

- ❑ Tumor mass
- ❑ Hypercalcemia
- ❑ Bence Jones proteinemia
- ❑ Renal impairment (stage B disease or creatinine level >2 mg/dL at diagnosis)

The prognosis by treatment is as follows:

- ❑ Conventional therapy: Overall survival is approximately 3 years, and event-free survival is less than 2 years.
- ❑ High-dose chemotherapy with stem-cell transplantation: The overall survival rate is greater than 50% at 5 years.

Bacterial infection is the leading cause of death in patients with myeloma.

A study by Larsen et al found that a significant reduction in plasma cell proliferation in patients with newly diagnosed MM is an important predictor of survival.

Patient Education

Patient education is very important in the management of MM. The International Myeloma Foundation (IMF) offers educational resources, a quarterly newsletter, and conferences.

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1. <http://emedicine.medscape.com>
2. <http://myoclinic.com>

Middle East Respiratory Syndrome is a viral respiratory illness. It is caused by a coronavirus called MERS-CoV. It was first reported in Saudi Arabia in 2012. Lab-confirmed MERS cases are also found in Oman, Qatar, Kuwait, Jordan, Tunisia, UAE, France, Italy and UK. On May 29, 2013, the World Health Organization warned that the MERS-CoV virus is a threat to the entire world.

Causative organism

MERS-CoV is a positive-sense, single-stranded, enveloped RNA virus. It is used to be called “novel coronavirus” as it is different from other coronaviruses that have been found previously. Other names of MERS-CoV are London1-novel CoV 2012, nCoV, human coronavirus-Erasmus Medical Center (HCoV-EMC). In humans, MERS-CoV has a strong tropism for non-ciliated bronchial epithelial cells. It has been shown to evade innate immune responses effectively and antagonize interferon (IFN) production in these cells. This tropism is unique in that most respiratory viruses target ciliated cells.

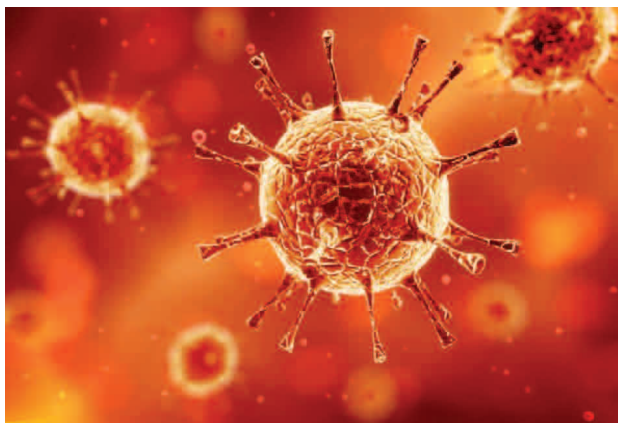


Figure : MERS Virus

Transmission

MERS-CoV is likely to be of animal origin. It has been found in bat in Saudi Arabia. In August, 2013, the source of the virus was traced to an Egyptian tomb bat found in a building in close proximity to the index-patient's home. The virus recovered from the bat was a 100% genetic match to the virus isolated from the index-patient. The virus has been found in camels in Qatar and in a few other countries where camels have been tested positive for antibodies to MERS-CoV, indicating they were previously infected with MERS-CoV or a closely related virus. On 13 February 2013, WHO stated that the risk of sustained person-to-person transmission appears to be very low. To date, no known routine contact exists between humans and bats. On July 22, 2013, the World Organization for Animal Health (OIE) announced that currently there is no strong evidence to suggest that camels are the source of infection for human cases of MERS. There is a potential danger in that it is possible for the virus to mutate into a strain that does transmit from person to person.

Clinical features

Most people who have been confirmed to have MERS-CoV infection developed severe acute respiratory illness usually within 14 days after spread. Main symptoms were fever, cough and shortness of breath. About half of these people died. Some reported as having a mild respiratory illness.

Laboratory testing

The recommended clinical samples for MERS-CoV testing on persons under investigation are respiratory tract samples (nasopharyngeal swab, broncho-alveolar lavage), urine, EDTA-blood, stool if gastrointestinal symptoms are present, acute and convalescent (21 to 28 days after illness onset) serology. Polymerase chain reaction is very effective to diagnose MERS-CoV.

Treatment

Currently, there are no specific treatments recommended for illness caused by MERS-CoV. Medical care is supportive and to help relieve symptoms. There is no vaccine for MERS-CoV.

Prevention of MERS-CoV infection

- Travelers to countries in or near the Arabian Peninsula should follow standard precautions. Hands should be washed with soap and water for at least 20 seconds. Nose and mouth should be covered with tissue paper during coughing or sneezing which must be discarded in the trash. Eyes, nose and mouth should not be touched with unwa-shed hands. Close contact such as kissing, sharing cups, or sharing eating utensils, with sick people must be avoided. Frequently touched surfaces, such as toys, door-locks should be cleaned frequently.
- Healthcare personnel should follow personal protective measures. Gloves, gowns, goggles or face shield should be used. Filtering face-piece respirator should be used upon entry into patient rooms or care areas. Upon exit from the patient room or care area, all protective equipments should be removed and either discarded or for re-useable protective equipments, cleaned and disinfected according to the manufacturer's reprocessing instructions.

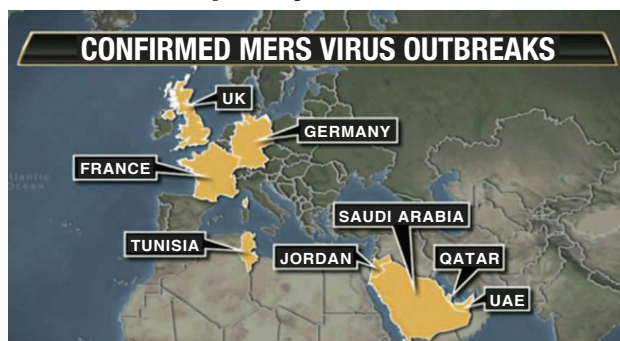


Figure : MERS Virus Outbreaks

- Infected patient should be placed in airborne infection isolation room (AIIR). If an AIIR is not available, the patient should be transferred as soon as feasible to a facility where an AIIR is available. Pending transfer, a facemask must be placed on the patient and he/she must be isolated in a single-patient room with the door closed. The patient should not be placed in any room where room exhaust is re-circulated without high-efficiency particulate air (HEPA) filtration. The number of personnel entering the room should be minimized.

References :

1. www.cdc.gov/coronavirus/mers
2. www.who.int/csr/disease/coronavirus_infection/MERS-CoV
3. en.wikipedia.org/wiki/Middle_East_respiratory_syndrome_coronavirus

Test Yourself - 33

Correct Answers :

1. a 2. b d 3. b 4. b 5. b 6. a c

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Test Yourself - 34

1. The followings are true for Multiple Myeloma except:

- Bone marrow microenvironment of tumor cells plays a pivotal role in the pathogenesis of myelomas.
- The diagnosis is incidental in 50% cases.
- Carpal tunnel syndrome is a common complication of myeloma.
- Anemia is the most common cause of weakness in patient with Multiple myeloma.

2. All the followings are correct for Glaucoma except:

- This can permanently damage vision in the affected eyes and lead to blindness, if untreated.
- Raised IOP (more than 21mmHG) is the most important and only modifiable risk factor for glaucoma.
- Glaucoma patients should consider themselves at risk of falls.
- Argon Laser Trabeculoplasty may be used to cure open-angle glaucoma.

3. All the below are true for Middle East Respiratory Syndrome except:

- It was first reported in Saudi Arabia in 2011.
- Most people who have been confirmed to have this infection developed severe acute respiratory illness.
- Currently, there are not specific treatments recommended for this illness.
- Polymerase chain reaction is very effective to diagnose MERS-Cov.

4. All the followings are correct for Drug Induced Kidney Injury except:

- Drugs cause approximately 20% of community and hospital acquired episodes of acute renal failure.
- The longer the duration of the use of NSAIDs, the more severe is the injury.
- Penicillins and cephalosporins may cause generalized allergic hypersensitivity reaction without involvements of kidneys.
- Ionic contrast media typically, but not always, have more side effects.

5. The followings are right for Multiple Myeloma except:

- International Staging System of the International Myeloma Working Group is based on three stages.
- Renal failure and insufficiency are seen in 75% of patients with Multiple myeloma.
- Patients with Multiple myeloma typically receive chemotherapy.
- It is a heterogeneous disease, with survival ranging from 01 year to more than 10 years.

6. All the followings are correct for Drug Induced Kidney Injury except:

- Aminoglycosides, tacrolimus are not inherently nephrotoxic.
- NSAIDs, ACEI or ARB can interfere with the kidneys' ability to auto regulate glomerular pressure.
- Cisplatin and carboplatin can cause dose-related direct cellular toxicity.
- Proton pump inhibitors are continuously being recognized as contributing to acute interstitial nephritis.

Soon our officials will be visiting you with a token of our appreciation

Siglita™

Sitagliptin

100 mg Tablet
50 mg Tablet

Signifies effective glycemetic control even with CKD



Dosage Guideline

Starting dose is 100 mg once daily, can be taken with or without food.

Dosage adjustment in patients with Moderate, Severe and End-stage Renal Disease (ESRD)

Moderate	Severe and ESRD
CrCl 30 to <50 mL/min	CrCl <30 mL/min
Dose: 50 mg once daily	Dose: 25 mg once daily

Nexum®

Esomeprazole

20 mg Tablet & Capsule
40 mg Tablet & Capsule
40 mg IV Injection

Superb acid control for 24 hours

- Active isomer of Omeprazole
- Superior to older PPIs for the management of GERD
- Effectively relieves night-time heart burn
- US FDA Pregnancy Category 'B'

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Locular™ Plus

Brimonidine 0.2% and Timolol 0.5% Eye Drops



« Power to pull down IOP with convenience »

- Provides combined effort to achieve IOP goal
- Reduces IOP more effectively than Brimonidine or Timolol alone
- Requires only 1 drop instead of two
- Manufactured in US FDA-compliant ophthalmic manufacturing facility

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