VOLUME - VIII
ISSUE - XLVIII
NOV / DEC 2011

The Crux

BIMONTHLY FORUM FOR THE LABORATARIANS

CONTENTS

Editorial

Which Disease is known as “PODAGRA” and which disease has been referred to as the rich man’s disease? Well you see it quite often in your practice. It is Gout (also known as podagra when it involves the big toe) is a medical condition usually characterized by recurrent attacks of acute inflammatory arthritis—a red, tender, hot, swollen joint. The metatarsal-phalangeal joint at the base of the big toe is the most commonly affected (approximately 50% of cases). However, it may also present as tophi, kidney stones, or urate nephropathy. It is caused by elevated levels of uric acid in the blood which crystallize and are deposited in joints, tendons, and surrounding tissues.

Diagnosis is confirmed clinically by the visualization of the characteristic crystals in joint fluid. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, or colchicine improves symptoms. Once the acute attack has subsided, levels of uric acid are usually lowered via lifestyle changes, and in those with frequent attacks allopurinol or probenecid provide long-term prevention.

Gout has increased in frequency in recent decades. The increase is believed to be due to increasing risk factors in the population, such as metabolic syndrome, longer life expectancy and changes in diet. In the United States, gout is twice as likely in African American males as it is in European Americans. Rates are high among the peoples of the Pacific Islands and the Māori of New Zealand, but rare in Australian aborigines, despite a higher mean concentration of serum uric acid in the latter group. It has become common in China, Polynesia, and urban sub-Saharan Africa. Some studies have found attacks of gout occur more frequently in the spring. This has been attributed to seasonal changes in diet, alcohol consumption, physical activity, and temperature. In India about 2% of the population at some time or the other during their life time suffers from Gout.

The word *gout* was initially used by Randolphus of Bocking, around 1200 AD. It is derived from the Latin word *gutta*, meaning "a drop" (of liquid). According to the Oxford English Dictionary, this is derived from humorism and "the notion of the 'dropping' of a morbid material from the blood in and around the joints". Gout has, however, been known since antiquity. Historically, it has been referred to as "the king of diseases and the disease of kings" or "rich man's disease". The first documentation of the disease is from Egypt in 2,600 BC in a description of arthritis of the big toe. The Greek physician Hippocrates around 400 BC commented on it in his *Aphorisms*, noting its absence in eunuchs and premenopausal women. Aulus Cornelius Celsus (30 AD) described the linkage with alcohol, later onset in women, and associated kidney problems. The **“DISEASE DIAGNOSIS”** segment covers all clinico-diagnostic aspects of Gout in ample detail.

Related to lifestyle and personal habits is consumption of ALCOHOL. A later complication of this vice is “Alcoholic Liver Disease”. **“INTERPRETATION”** portion of this issue starts with a case history and clearly describes all related aspects.

“TROUBLESHOOTING” outlines the Non Gynecological Cytology Practice Guidelines for you. Quality control/ assurance aspects are considered in necessary depth.

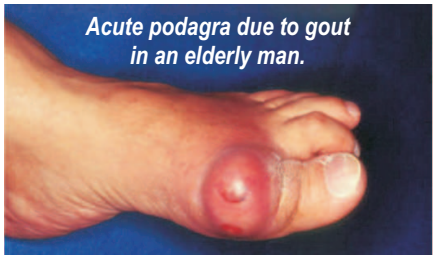
As always, **“BOUQUET”** has not been forgotten.

DISEASE DIAGNOSIS

GOUT

Introduction

Background: Gout is a common disorder of uric acid metabolism that can lead to deposition of monosodium urate (MSU) crystals in soft tissue, recurrent episodes of debilitating joint inflammation, and, if untreated, joint destruction and renal damage. Gout is definitively diagnosed based on the demonstration of urate crystals in aspirated synovial fluid. Improvements in early diagnosis and the availability of definitive treatment have significantly improved the prognosis of gout, as evidenced by the declining incidence of disabling chronic tophaceous gout. However, tophaceous gout may still develop because of misdiagnosis, poor management, medication intolerances, and/or poor patient compliance.



Acute podagra due to gout in an elderly man.

Pathophysiology: Although the presence of urate crystals in the soft and synovial tissues is a prerequisite for a gouty attack, the fact that urate crystals can also be found in synovial fluid in the absence of joint inflammation suggests that the mere presence of intrasynovial urate crystals is not sufficient to cause flares of gouty arthritis. One explanation for this may lie in the observation that clumps or microtophi of highly negatively charged and reactive MSU crystals are normally coated with serum proteins (apolipoprotein [apo] E or apo B) that physically inhibit the binding of MSU crystals to cell receptors. A gout attack may be triggered by either a release of uncoated crystals (eg, due to partial dissolution of a microtophus caused by changing serum urate levels) or precipitation of crystals in a supersaturated microenvironment (eg, release of urate due to cellular damage). From either source, naked urate crystals are then believed to interact with intracellular and surface receptors of local dendritic cells and macrophages, serving as a danger signal to activate the innate immune system. This interaction may be enhanced by immunoglobulin G (IgG) binding. Triggering of these receptors, including Toll-like receptors, NALP3 inflammasomes, and the triggering receptors expressed on myeloid cells (TREMs) by MSU, results in the production of interleukin (IL)–1, which in turn initiates the production of a cascade of pro-inflammatory cytokines, including IL-6, IL-8, neutrophil chemotactic factors, and tumor necrosis factor (TNF)–alpha. Neutrophil phagocytosis leads to another burst of inflammatory mediator production. Subsidence of an acute gout attack is due to multiple mechanisms, including the clearance of damaged neutrophils, recoating of urate crystals, and the production of anti-inflammatory cytokines including, IL-1RA, IL-10, and transforming growth factor (TGF)–beta.

Frequency

International: Gout has a worldwide distribution; regional differences may reflect environmental, dietary, and genetic influences.

Mortality/Morbidity: Gout is associated with considerable morbidity. Acute episodes of gout often lead to incapacitation. Untreated chronic tophaceous gout can lead to severe joint destruction. MSU deposition in the kidney can result in inflammation and fibrosis, leading to reduced renal function or chronic renal nephropathy. Hyperuricemia and gout are associated with an increased overall likelihood of mortality. Whether this is directly attributable to hyperuricemia or gout or to gout-associated diseases (eg, insulin resistance, type 2 diabetes mellitus, abdominal obesity, hypercholesterolemia, hypertension) has been much debated. Although no evidence has shown that gout or hyperuricemia causes any of these disorders, elevated urate levels have been shown to correlate with blood pressure in adolescents, and, among middle-aged men, hyperuricemia with gout was a significant independent risk for death due to cardiovascular disease. In a more recent study, it has been shown that gout, but not hyperuricemia, is associated with higher risk of death from all causes and cardiovascular diseases.

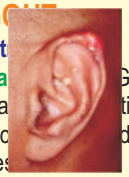
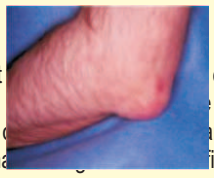
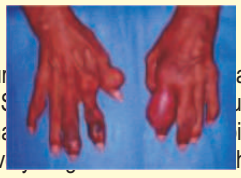
Race: Gout is slightly more prevalent in blacks than in whites.

Sex: The prevalence of gout is 13.6 cases per 1000 men and 6.4 cases per 1000 women. This difference is largely a consequence of age at onset because estrogenic hormones have a mild uricosuric effect; therefore, gout is unusual in premenopausal women.

Age: As a rule, uric acid levels are elevated for 20 years before the onset of gout. In men, uric acid levels rise at puberty, and the peak age of onset of gout in men is in the fourth to sixth decade of life. In women, uric acid levels rise at menopause, and peak age of onset in women is in the sixth to eighth decade of life. Gout is unlikely to present in premenopausal women or in men younger than 30 years who do not have renal insufficiency or a genetic abnormality of purine metabolism (eg, hypoxanthine-guanine phosphoribosyltransferase deficiency, phosphoribosylpyrophosphate synthetase superactivity). The higher prevalence of gout in elderly persons may also reflect an increased prevalence of metabolic syndrome, high rates of diuretic treatment for hypertension and congestive heart failure, and the use of low-dose acetylsalicylic acid. Tophi are typically detectable clinically approximately 10 years after the first gout attack. Cyclosporin A can cause an accelerated form of gout, even in premenopausal women, that can present after only a few years of hyperuricemia, particularly if the patient is also receiving diuretics.

Clinical

History: Acute monoarticular arthritis is the initial presentation of gout in 90% of patients. In early gout, only 1 or 2 joints are usually involved. Typically, they are the smaller, lower-extremity joints. Podagra (inflammation of the first metatarsophalangeal joint) is the initial joint manifestation in 50% of cases. Eventually, it is involved in 90% of cases. Podagra is not synonymous with gout. Podagra may be observed in patients with pseudogout, sarcoidosis, gonococcal arthritis, psoriatic arthritis, and reactive arthritis. The attacks begin abruptly and reach maximum intensity within 8-12 hours. The joints are red, hot, and exquisitely tender; even a bed sheet on the swollen joint is uncomfortable. Untreated, the first attacks resolve spontaneously in less than 2 weeks. A history of intermittent inflammatory arthritis, in which the joints return to normal between attacks, is typically caused by crystalline disorders and is characteristic of gouty arthritis early in its course. Gout initially presents as polyarticular arthritis in 10% of patients. Elderly women, particularly women with renal insufficiency on a thiazide diuretic, can develop polyarticular arthritis as the first manifestation of gout. These attacks may occur in coexisting Heberden and Bouchard nodes. Such patients may also develop tophi more quickly, occasionally without prior episodes of acute gouty arthritis. The pattern of symptoms in untreated gout change over time. The attacks become more polyarticular. Although more joints may become involved, inflammation in a given joint may become less intense. More proximal and upper-extremity joints become involved. Attacks occur more frequently and last longer. Eventually, patients may develop chronic polyarticular arthritis, sometimes nearly symmetrical, that can resemble rheumatoid arthritis. Indeed, chronic polyarticular arthritis that began as an intermittent arthritis should prompt consideration of a crystalline disorder in the differential diagnoses. Although gout typically causes joint inflammation, it can also cause inflammation in other synovial-based structures such as bursae and tendons. Tophi are collections of urate crystals in the soft tissues. They develop in more than half of patients with untreated gout and may be reported as lumps or nodules. While the classic location of tophi is along the helix of the ear, they can be found in multiple locations, including the fingers, toes, in the olecranon bursae, and along the olecranon, where they can resemble rheumatoid nodules. The finding of a rheumatoid nodule in a patient with a negative rheumatoid factor result or a history of drainage from a nodule should prompt consideration of gout in the differential diagnoses. Tophi are not commonly found during the first gout episode. They tend to develop after 10 years in untreated patients who develop chronic gouty arthritis. Tophi tend to develop earlier in women, particularly those receiving diuretics.

GO
Int
Ba Gout of ur an
lea tion (MS ue,
rec des amma int
des rena finitiv he
demonstration of urate crystals in aspirated synovial fluid. Improvements in early diagnosis and the availability of definitive treatment have significantly improved the prognosis of gout, as evidenced by the declining incidence of disabling chronic tophaceous gout. However, tophaceous gout may still develop because of misdiagnosis, poor management, medication intolerances, and/or poor patient compliance.

Pathophysiology: Although the presence of urate crystals in the soft and synovial tissues is a prerequisite for a gouty attack, the fact that urate crystals can also be found in synovial fluid in the absence of joint inflammation suggests that the mere presence of intrasynovial urate crystals is not sufficient to cause flares of gouty arthritis. One explanation for this may lie in the observation that clumps or microtophi of highly negatively charged and reactive MSU crystals are normally coated with serum proteins (apolipoprotein [apo] E or apo B) that physically inhibit the binding of MSU crystals to cell receptors. A gout attack may be triggered by either a release of uncoated crystals (eg, due to partial dissolution of a microtophus caused by changing serum urate levels) or precipitation of crystals in a supersaturated microenvironment (eg, release of urate due to cellular damage). From either source, naked urate crystals are then believed to interact with intracellular and surface receptors of local dendritic cells and macrophages, serving as a danger signal to activate the innate immune system. This interaction may be enhanced by immunoglobulin G (IgG) binding. Triggering of these receptors, including Toll-like receptors, NALP3 inflammasomes, and the triggering receptors expressed on myeloid cells (TREMs) by MSU, results in the production of interleukin (IL)–1, which in turn initiates the production of a cascade of pro-inflammatory cytokines, including IL-6, IL-8, neutrophil chemotactic factors, and tumor necrosis factor (TNF)–alpha. Neutrophil phagocytosis leads to another burst of inflammatory mediator production. Subsidence of an acute gout attack is due to multiple mechanisms, including the clearance of damaged neutrophils, recoating of urate crystals, and the production of anti-inflammatory cytokines including, IL-1RA, IL-10, and transforming growth factor (TGF)–beta.

Frequency

International: Gout has a worldwide distribution; regional differences may reflect environmental, dietary, and genetic influences.

Mortality/Morbidity: Gout is associated with considerable morbidity. Acute episodes of gout often lead to incapacitation. Untreated chronic tophaceous gout can lead to severe joint destruction. MSU deposition in the kidney can result in inflammation and fibrosis, leading to reduced renal function or chronic renal nephropathy. Hyperuricemia and gout are associated with an increased overall likelihood of mortality. Whether this is directly attributable to hyperuricemia or gout or to gout-associated diseases (eg, insulin resistance, type 2 diabetes mellitus, abdominal obesity, hypercholesterolemia, hypertension) has been much debated. Although no evidence has shown that gout or hyperuricemia causes any of these disorders, elevated urate levels have been shown to correlate with blood pressure in adolescents, and, among middle-aged men, hyperuricemia with gout was a significant independent risk for death due to cardiovascular disease. In a more recent study, it has been shown that gout, but not hyperuricemia, is associated with higher risk of death from all causes and cardiovascular diseases.

Race: Gout is slightly more prevalent in blacks than in whites.

Sex: The prevalence of gout is 13.6 cases per 1000 men and 6.4 cases per 1000 women. This difference is largely a consequence of age at onset because estrogenic hormones have a mild uricosuric effect; therefore, gout is unusual in premenopausal women.

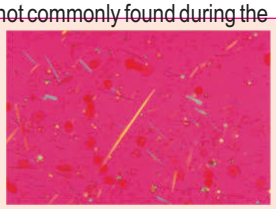
Age: As a rule, uric acid levels are elevated for 20 years before the onset of gout. In men, uric acid levels rise at puberty, and the peak age of onset of gout in men is in the fourth to sixth decade of life. In women, uric acid levels rise at menopause, and peak age of onset in women is in the sixth to eighth decade of life. Gout is unlikely to present in premenopausal women or in men younger than 30 years who do not have renal insufficiency or a genetic abnormality of purine metabolism (eg, hypoxanthine-guanine phosphoribosyltransferase deficiency, phosphoribosylpyrophosphate synthetase superactivity). The higher prevalence of gout in elderly persons may also reflect an increased prevalence of metabolic syndrome, high rates of diuretic treatment for hypertension and congestive heart failure, and the use of low-dose acetylsalicylic acid. Tophi are typically detectable clinically approximately 10 years after the first gout attack. Cyclosporin A can cause an accelerated form of gout, even in premenopausal women, that can present after only a few years of hyperuricemia, particularly if the patient is also receiving diuretics.

Clinical

History: Acute monoarticular arthritis is the initial presentation of gout in 90% of patients. In early gout, only 1 or 2 joints are usually involved. Typically, they are the smaller, lower-extremity joints. Podagra (inflammation of the first metatarsophalangeal joint) is the initial joint manifestation in 50% of cases. Eventually, it is involved in 90% of cases. Podagra is not synonymous with gout. Podagra may be observed in patients with pseudogout, sarcoidosis, gonococcal arthritis, psoriatic arthritis, and reactive arthritis. The attacks begin abruptly and reach maximum intensity within 8-12 hours. The joints are red, hot, and exquisitely tender; even a bed sheet on the swollen joint is uncomfortable. Untreated, the first attacks resolve spontaneously in less than 2 weeks. A history of intermittent inflammatory arthritis, in which the joints return to normal between attacks, is typically caused by crystalline disorders and is characteristic of gouty arthritis early in its course. Gout initially presents as polyarticular arthritis in 10% of patients. Elderly women, particularly women with renal insufficiency on a thiazide diuretic, can develop polyarticular arthritis as the first manifestation of gout. These attacks may occur in coexisting Heberden and Bouchard nodes. Such patients may also develop tophi more quickly, occasionally without prior episodes of acute gouty arthritis. The pattern of symptoms in untreated gout change over time. The attacks become more polyarticular. Although more joints may become involved, inflammation in a given joint may become less intense. More proximal and upper-extremity joints become involved. Attacks occur more frequently and last longer. Eventually, patients may develop chronic polyarticular arthritis, sometimes nearly symmetrical, that can resemble rheumatoid arthritis. Indeed, chronic polyarticular arthritis that began as an intermittent arthritis should prompt consideration of a crystalline disorder in the differential diagnoses. Although gout typically causes joint inflammation, it can also cause inflammation in other synovial-based structures such as bursae and tendons. Tophi are collections of urate crystals in the soft tissues. They develop in more than half of patients with untreated gout and may be reported as lumps or nodules. While the classic location of tophi is along the helix of the ear, they can be found in multiple locations, including the fingers, toes, in the olecranon bursae, and along the olecranon, where they can resemble rheumatoid nodules. The finding of a rheumatoid nodule in a patient with a negative rheumatoid factor result or a history of drainage from a nodule should prompt consideration of gout in the differential diagnoses. Tophi are not commonly found during the

Fluid obtained from a tophaceous deposit in a patient with gout.

Strongly negative birefringent, needle-shaped crystals diagnostic of gout obtained from an acutely inflamed joint.



Needles of urate on polarizing microscopy.

GOUT

Introduction

Background: Gout is a common disorder of uric acid metabolism that can lead to deposition of monosodium urate (MSU) crystals in soft tissue, recurrent episodes of debilitating joint inflammation, and, if untreated, joint destruction and renal damage. Gout is definitively diagnosed based on the demonstration of urate crystals in aspirated synovial fluid. Improvements in early diagnosis and the availability of definitive treatment have significantly improved the prognosis of gout, as evidenced by the declining incidence of disabling chronic tophaceous gout. However, tophaceous gout may still develop because of misdiagnosis, poor management, medication intolerances, and/or poor patient compliance.

Pathophysiology: Although the presence of urate crystals in the soft and synovial tissues is a prerequisite for a gouty attack, the fact that urate crystals can also be found in synovial fluid in the absence of joint inflammation suggests that the mere presence of intrasynovial urate crystals is not sufficient to cause flares of gouty arthritis. One explanation for this may lie in the observation that clumps or microtophi of highly negatively charged and reactive MSU crystals are normally coated with serum proteins (apolipoprotein [apo] E or apo B) that physically inhibit the binding of MSU crystals to cell receptors. A gout attack may be triggered by either a release of uncoated crystals (eg, due to partial dissolution of a microtophus caused by changing serum urate levels) or precipitation of crystals in a supersaturated microenvironment (eg, release of urate due to cellular damage). From either source, naked urate crystals are then believed to interact with intracellular and surface receptors of local dendritic cells and macrophages, serving as a danger signal to activate the innate immune system. This interaction may be enhanced by immunoglobulin G (IgG) binding. Triggering of these receptors, including Toll-like receptors, NALP3 inflammasomes, and the triggering receptors expressed on myeloid cells (TREMs) by MSU, results in the production of interleukin (IL)–1, which in turn initiates the production of a cascade of pro-inflammatory cytokines, including IL-6, IL-8, neutrophil chemotactic factors, and tumor necrosis factor (TNF)–alpha. Neutrophil phagocytosis leads to another burst of inflammatory mediator production. Subsidence of an acute gout attack is due to multiple mechanisms, including the clearance of damaged neutrophils, recoating of urate crystals, and the production of anti-inflammatory cytokines including, IL-1RA, IL-10, and transforming growth factor (TGF)–beta.

Frequency

International: Gout has a worldwide distribution; regional differences may reflect environmental, dietary, and genetic influences.

Mortality/Morbidity: Gout is associated with considerable morbidity. Acute episodes of gout often lead to incapacitation. Untreated chronic tophaceous gout can lead to severe joint destruction. MSU deposition in the kidney can result in inflammation and fibrosis, leading to reduced renal function or chronic renal nephropathy. Hyperuricemia and gout are associated with an increased overall likelihood of mortality. Whether this is directly attributable to hyperuricemia or gout or to gout-associated diseases (eg, insulin resistance, type 2 diabetes mellitus, abdominal obesity, hypercholesterolemia, hypertension) has been much debated. Although no evidence has shown that gout or hyperuricemia causes any of these disorders, elevated urate levels have been shown to correlate with blood pressure in adolescents, and, among middle-aged men, hyperuricemia with gout was a significant independent risk for death due to cardiovascular disease. In a more recent study, it has been shown that gout, but not hyperuricemia, is associated with higher risk of death from all causes and cardiovascular diseases.

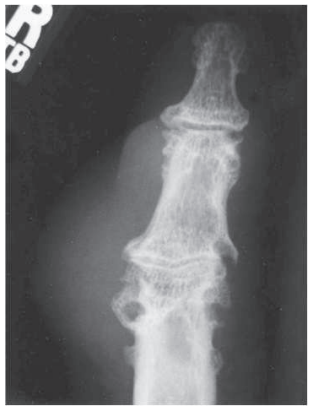
Race: Gout is slightly more prevalent in blacks than in whites.

Sex: The prevalence of gout is 13.6 cases per 1000 men and 6.4 cases per 1000 women. This difference is largely a consequence of age at onset because estrogenic hormones have a mild uricosuric effect; therefore, gout is unusual in premenopausal women.

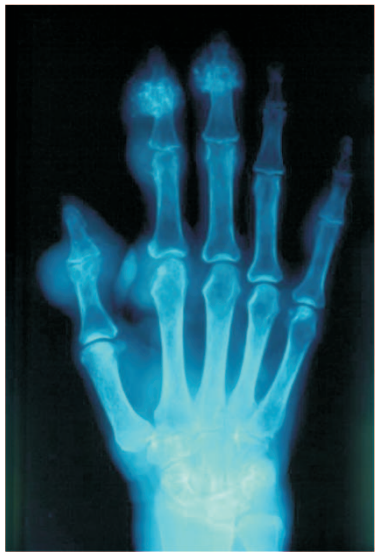
Age: As a rule, uric acid levels are elevated for 20 years before the onset of gout. In men, uric acid levels rise at puberty, and the peak age of onset of gout in men is in the fourth to sixth decade of life. In women, uric acid levels rise at menopause, and peak age of onset in women is in the sixth to eighth decade of life. Gout is unlikely to present in premenopausal women or in men younger than 30 years who do not have renal insufficiency or a genetic abnormality of purine metabolism (eg, hypoxanthine-guanine phosphoribosyltransferase deficiency, phosphoribosylpyrophosphate synthetase superactivity). The higher prevalence of gout in elderly persons may also reflect an increased prevalence of metabolic syndrome, high rates of diuretic treatment for hypertension and congestive heart failure, and the use of low-dose acetylsalicylic acid. Tophi are typically detectable clinically approximately 10 years after the first gout attack. Cyclosporin A can cause an accelerated form of gout, even in premenopausal women, that can present after only a few years of hyperuricemia, particularly if the patient is also receiving diuretics.

Clinical

History: Acute monoarticular arthritis is the initial presentation of gout in 90% of patients. In early gout, only 1 or 2 joints are usually involved. Typically, they are the smaller, lower-extremity joints. Podagra (inflammation of the first metatarsophalangeal joint) is the initial joint manifestation in 50% of cases. Eventually, it is involved in 90% of cases. Podagra is not synonymous with gout. Podagra may be observed in patients with pseudogout, sarcoidosis, gonococcal arthritis, psoriatic arthritis, and reactive arthritis. The attacks begin abruptly and reach maximum intensity within 8-12 hours. The joints are red, hot, and exquisitely tender; even a bed sheet on the swollen joint is uncomfortable. Untreated, the first attacks resolve spontaneously in less than 2 weeks. A history of intermittent inflammatory arthritis, in which the joints return to normal between attacks, is typically caused by crystalline disorders and is characteristic of gouty arthritis early in its course. Gout initially presents as polyarticular arthritis in 10% of patients. Elderly women, particularly women with renal insufficiency on a thiazide diuretic, can develop polyarticular arthritis as the first manifestation of gout. These attacks may occur in coexisting Heberden and Bouchard nodes. Such patients may also develop tophi more quickly, occasionally without prior episodes of acute gouty arthritis. The pattern of symptoms in untreated gout change over time. The attacks become more polyarticular. Although more joints may become involved, inflammation in a given joint may become less intense. More proximal and upper-extremity joints become involved. Attacks occur more frequently and last longer. Eventually, patients may develop chronic polyarticular arthritis, sometimes nearly symmetrical, that can resemble rheumatoid arthritis. Indeed, chronic polyarticular arthritis that began as an intermittent arthritis should prompt consideration of a crystalline disorder in the differential diagnoses. Although gout typically causes joint inflammation,



Radiograph of erosions with overhanging edges.



Plain radiograph showing chronic tophaceous gouty arthritis in the hands.

INTERPRETATION

ALCOHOLIC LIVER DISEASE

A 42-year-old man presents with low-grade fever, anorexia, dark urine, light-colored stools, and right upper quadrant aching discomfort of 2 weeks' duration. He indicates that he has consumed a pint of whiskey daily for the past 10 years and denies use of illicit drugs or exposure to hepatitis. His physical examination reveals sclera icterus, cutaneous jaundice, proximal muscle wasting, asterixis, a palpable liver and spleen, and peripheral edema. Laboratory studies include an aspartate aminotransferase (AST) of 102 IU, a normal alanine aminotransferase (ALT), an elevated alkaline phosphatase, bilirubin of 6.5 mg/dL, and prothrombin time of 19 seconds (control of 12 seconds). On the basis of his history of chronic alcohol consumption, fever, hepatosplenomegaly, cholestasis and an AST/ALT ratio of greater than 2 to 1, you make a presumptive diagnosis of acute alcoholic hepatitis.

Alcoholic Liver Disease:

Chronic alcoholism is a frequent cause of liver disease and a common cause of cirrhosis in Western countries. The risk of developing cirrhosis is increased by coexisting hepatitis C virus (HCV) infection. No specific amount of ethanol consumption is associated with liver injury, although it typically follows high daily intake of 10 to 20 years' duration or longer because patients with sustained blood alcohol levels are most likely to develop liver disease. When alcoholic cirrhosis develops, continued ethanol consumption worsens the prognosis. Chronic alcohol consumption not only causes liver disease (fatty liver, alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma), it also increases the risk for tumors such as squamous cell carcinomas eg, pharyngeal, esophageal). Although alcoholic liver disease is associated with excessive ethanol intake, it is not simply a consequence of ethanol per se because end-stage liver disease develops in only 10% of alcoholics. Acetaldehyde, the proximate metabolite of ethanol, may be the metabolite responsible for the development of alcoholic liver disease.

Ethanol Metabolism:

Ethanol is principally metabolized by hepatocyte alcohol dehydrogenase (ADH) to acetaldehyde, which is further metabolized by aldehyde dehydrogenase (ALDH) to acetate. The microsomal cytochrome P450 system (CYP2E1) plays a greater role in the metabolism of ethanol when there is excessive alcohol consumption. Catalase has a minor role in ethanol metabolism. Variants of both ADH and ALDH could be related to the development of liver disease. More rapid formation of acetaldehyde by ADH enzyme variants or a reduction in clearance of acetaldehyde by variants of ALDH (eg, ALDH2*2) could increase the exposure of hepatocytes to highly reactive acetaldehyde.

Epidemiology:

Approximately 6%-7% of Americans are alcoholics (11% of men and 6% of women and alcoholic hepatitis and cirrhosis will develop in approximately 10% of chronic alcoholics. What separates those who develop advanced liver disease from those who do not is unclear. Suggested factors include gender, ethnicity, presence of obesity or hepatic iron overload, and the daily quantity of ethanol consumed. Genetic predisposition may play a role in alcohol dependence. Women are at greater risk than men for development of cirrhosis. The risk for cirrhosis in women develops at 7-13 drinks per week and for men, at 14-27 drinks per week. Blacks and Hispanics and Asians may be at higher risk for cirrhosis mortality.Other factors that may be important in the development of alcoholic hepatitis and cirrhosis include hepatocyte damage related to: Immune cytokines released in response to ethanol metabolites, or acetaldehyde-protein adducts; An altered redox state or hypermetabolic state related to ethanol metabolism; Formation of free radicals during ethanol metabolism, producing oxidative stress or lipid peroxidation; Increased endotoxin levels as a consequence of enhanced small intestinal permeability, concurrent nutritional deficiency or coexisting hepatitis C[11,12]; and Concurrent nutritional deficiency or coexisting hepatitis C. The precise mechanism(s) causing advanced alcoholic liver disease remain unknown.

Fatty Metamorphosis of the Liver:

Fatty liver is the most common hepatic manifestation of chronic alcoholism. Fatty change of hepatocytes can develop within 2 days of ethanol excess and resolve within 2 weeks of discontinuation of ethanol. Patients with alcoholic fatty livers are typically asymptomatic although they may have mild right upper quadrant pain and hepatomegaly. Aminotransferases can be elevated and gamma-glutamyl transpeptidase (GGT) levels are often increased as a result of ethanol-induced microsomal enzyme activity. Alcoholic fatty liver can be difficult to differentiate from non-alcoholic fatty liver disease. A careful history for alcohol consumption, lack of findings of metabolic syndrome, an AST/ALT ratio > 2, and a markedly elevated GGT suggest alcoholic fatty liver. Hepatic ultrasound can identify changes consistent with fatty liver and a liver biopsy specimen, if obtained, demonstrates macrovesicular fat of perivenular (centrizonal) hepatocytes. In an occasional alcoholic patient, severe microvesicular fatty change of hepatocytes (alcoholic foamy degeneration) may develop as a consequence of mitochondrial dysfunction associated with severe hepatic encephalopathy and hyperbilirubinemia, and this patient has an increased risk for death. The treatment of patients with alcoholic fatty liver is cessation of ethanol consumption and provision of nutritional support for patients with coexisting nutritional deficiencies.

Alcoholic Hepatitis:

Alcoholic hepatitis develops in approximately 10% of those with long-term daily ethanol consumption. Patients present with symptoms of fatigue, anorexia, fever, jaundice, weight loss, right upper quadrant pain, and an enlarged liver. Signs of hepatic decompensation including ascites and encephalopathy may be present. Occasionally an arterial bruit will be heard over the liver in the patient with alcoholic hepatitis. Hepatic bruits are also occasionally heard in patients with hepatocellular carcinoma.

Laboratory studies in alcoholic hepatitis:

Modest leukocytosis (12-14,000/mm3) but may occasionally present as a leukemoid reaction; AST/ALT > 2:1; Elevated alkaline phosphatase and GGT; Hypothrombinemia; Hyperbilirubinemia; Cholestasis; and Hypoalbuminemia.

Histology of alcoholic hepatitis:

Liver histology is characterized by perivenular hepatocellular necrosis and ballooning degeneration, macro- and microvesicular steatosis, and polymorphonuclear leukocyte inflammation with or without fibrosis or Mallory's hyaline. Hepatocellular necrosis; Ballooning degeneration of hepatocytes; Macro- and microvesicular steatosis/fatty metamorphosis of hepatocytes; Polymorphonuclear leukocyte inflammation; Cholestasis; Mallory's hyaline; and Pericellular fibrosis.

Fatty change of liver cells may or may not be present. Fibrosis is initially pericellular and progresses to bridging fibrosis. Alcoholic hepatitis is a clinically severe hepatic disorder with a 35%-45% mortality that correlates with the severity of associated malnutrition.

Alcoholic Cirrhosis:

Patients with alcoholic cirrhosis may be asymptomatic or present with symptoms and signs of end-stage liver disease and portal hypertension including ascites, encephalopathy, or variceal hemorrhage. Laboratory findings include an elevated prothrombin time, abnormal liver tests and hypoalbuminemia. Hepatic ultrasound may identify a nodular, dense liver with evidence of portal hypertension including splenomegaly, portal vein enlargement, altered portal vein flows, and ascites. All patients with suspected alcoholic cirrhosis should undergo upper endoscopy to screen for esophageal varices.

Treatment of Alcoholic Liver Disease:

Abstinence from alcohol is the mainstay of treatment for alcoholic liver disease and it improves outcomes in all patients with alcoholic liver disease regardless of the severity of liver disease. Additional nutritional supplementation is often needed and all patients should be referred to alcohol treatment centers. For patients with mild fatty liver, fatty metamorphosis of hepatocytes will disappear within 2 weeks of ethanol cessation[and liver test results should rapidly normalize. For patients with

ALCOHOLIC LIVER DISEASE

A 42-year-old man presents with low-grade fever, anorexia, dark urine, light-colored stools, and right upper quadrant aching discomfort of 2 weeks' duration. He indicates that he has consumed a pint of whiskey daily for the past 10 years and denies use of illicit drugs or exposure to hepatitis. His physical examination reveals sclera icterus, cutaneous jaundice, proximal muscle wasting, asterixis, a palpable liver and spleen, and peripheral edema. Laboratory studies include an aspartate aminotransferase (AST) of 102 IU, a normal alanine aminotransferase (ALT), an elevated alkaline phosphatase, bilirubin of 6.5 mg/dL, and prothrombin time of 19 seconds (control of 12 seconds). On the basis of his history of chronic alcohol consumption, fever, hepatosplenomegaly, cholestasis and an AST/ALT ratio of greater than 2 to 1, you make a presumptive diagnosis of acute alcoholic hepatitis.

Alcoholic Liver Disease:

Chronic alcoholism is a frequent cause of liver disease and a common cause of cirrhosis in Western countries. The risk of developing cirrhosis is increased by coexisting hepatitis C virus (HCV) infection. No specific amount of ethanol consumption is associated with liver injury, although it typically follows high daily intake of 10 to 20 years' duration or longer because patients with sustained blood alcohol levels are most likely to develop liver disease. When alcoholic cirrhosis develops, continued ethanol consumption worsens the prognosis. Chronic alcohol consumption not only causes liver disease (fatty liver, alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma), it also increases the risk for tumors such as squamous cell carcinomas eg, pharyngeal, esophageal). Although alcoholic liver disease is associated with excessive ethanol intake, it is not simply a consequence of ethanol per se because end-stage liver disease develops in only 10% of alcoholics. Acetaldehyde, the proximate metabolite of ethanol, may be the metabolite responsible for the development of alcoholic liver disease.

Ethanol Metabolism:

Ethanol is principally metabolized by hepatocyte alcohol dehydrogenase (ADH) to acetaldehyde, which is further metabolized by aldehyde dehydrogenase (ALDH) to acetate. The microsomal cytochrome P450 system (CYP2E1) plays a greater role in the metabolism of ethanol when there is excessive alcohol consumption. Catalase has a minor role in ethanol metabolism. Variants of both ADH and ALDH could be related to the development of liver disease. More rapid formation of acetaldehyde by ADH enzyme variants or a reduction in clearance of acetaldehyde by variants of ALDH (eg, ALDH2*2) could increase the exposure of hepatocytes to highly reactive acetaldehyde.

Epidemiology:

Approximately 6%-7% of Americans are alcoholics (11% of men and 6% of women and alcoholic hepatitis and cirrhosis will develop in approximately 10% of chronic alcoholics. What separates those who develop advanced liver

BOUQUET

In Lighter Vein

Yukon Cornelius walks into a North Pole pub and clears his voice to the crowd of elven drinkers. He says, "I hear you elves are a bunch of hard drinkers. I'll give 500 gold to anybody in here who can drink 10 pints of extra stout back-to-back."

The room is quiet, and no one takes up Yukon's offer. One elf even leaves. Thirty minutes later the same elf who left shows back up and taps the prospector on the back. "Is your bet still good?" asks the elf.

Yukon says yes and asks the pub keep to line up 10 pints of extra stout. Immediately the elf tears into all 10 of the pint glasses, drinking them all back-to-back. The other pub patrons cheer as Yukon sits in amazement. He gives the elf the 500 gold and says, "If you don't mind me asking, where did you go for that 30 minutes you were gone?"

The elf replies, "Oh... I had to go to the pub down the street to see if I could do it first."

A doctor vacationing on the Riviera met an old lawyer friend and asked him what he was doing there. The lawyer replied, "Remember that lousy real estate I bought? Well, it caught fire, so here I am with the fire insurance proceeds. What are you doing here?" The doctor replied, "Remember that lousy real estate I had in Mississippi? Well, the river overflowed, and here I am with the flood insurance proceeds." The lawyer looked puzzled. "Gee," he asked, "how do you start a flood?"

On a group of beautiful deserted tropical islands in the middle of nowhere, the following people are suddenly stranded by, as you might expect, a shipwreck: 2 Italian men and 1 Italian woman; 2 French men and 1 French woman; 2 German men and 1 German woman; 2 Greek men and 1 Greek woman; 2 English men and 1 English woman; 2 Bulgarian men and 1 Bulgarian woman; 2 Japanese men and 1 Japanese woman; 2 Chinese men and 1 Chinese woman; 2 American men and 1 American woman; 2 Irish men and 1 Irish woman.

One month later on these same absolutely, stunningly beautiful desert (and deserted) Islands in the middle of nowhere, the following things have occurred: One Italian man killed the other Italian man for the Italian woman. The 2 French men and the French woman are living happily together in a menage-a-trois. The 2 German men have a strict weekly schedule of alternating visits with the German woman. The 2 Greek men are sleeping with each other and the Greek woman is cleaning and cooking for them. The 2 English men are waiting for someone to introduce them to the English woman. The 2 Bulgarian men took one look at the endless ocean, another long look at the Bulgarian woman, and started swimming...

The 2 Japanese men have faxed Tokyo and are awaiting instructions. The 2 Chinese men have set up a pharmacy, a liquor store, a restaurant, and a laundromat. And have got the woman pregnant in order to supply employees for the store. The 2 American men are contemplating the virtues of suicide because the American woman keeps endlessly complaining about her body, the true nature of feminism, how she can do everything they can do, the necessity of fulfillment, the equal division of household chores, how sand and palm trees make her look fat, how her last boyfriend respected her opinion and treated her nicer than they do, how her relationship with her mother is improving, and at least the taxes are low, and it isn't raining....

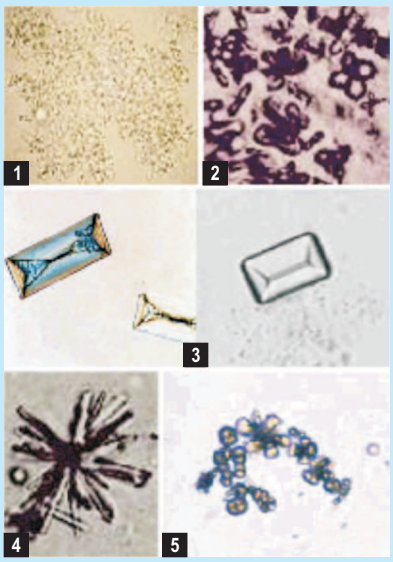
The 2 Irish men have divided the Island into North and South and set up a distillery. They do not remember if sex is in the picture, because it gets sort of foggy after the first few liters of coconut whiskey. But they are satisfied because at least the English aren't having any fun.

Wisdom Whispers

- "The devil dances in an empty pocket."
- "One poison is cured by another."
- "Weight and measure save a man toil."
- "To a young heart everything is sport."
- "Better leave than want."
- "Fortune helps fools."
- "No matter how long a log stays in the water it does not become a crocodile."
- "Not to oversee workmen, is to leave your purse open."
- "In a flat country a hillock thinks itself a mountain."
- "The chameleon changes color to match the earth, the earth doesn't change color to match the chameleon."

Brain Teasers

Identify the following crystals as found in alkaline urine



Answers: Crystals usually found in alkaline urine: (1) Amorphous phosphate, (2) Calcium carbonate, (3) Triple phosphate in urine, (4) Calcium phosphate, and (5) Ammonium urate crystals in urine

TROUBLESHOOTING

Nongynecological Cytology Practice Guidelines

Quality Control and Quality Assurance Practices

Quality control (QC) and quality assurance (QA) can be considered as the first two levels, respectively, in the hierarchical stages of quality. Quality control is defined as a system for verifying and maintaining a desired level of quality using operational techniques for an individual test or process. Quality control activities span the testing process, from pre-analytic (specimen collection and processing) through analytic (interpretive) and post-analytic (receipt of the report and analysis of results) phases. Quality assurance (QA) is defined as systematic monitoring of quality control results and quality practice parameters to assure that all systems are functioning in a manner appropriate to excellence in health care delivery. Quality assurance is a coordinated system designed to detect, control and prevent the occurrence of errors and, ultimately, to further a clinician's ability to appropriately care for his or her patient. The third stage, quality system, consists of the comprehensive and coordinated efforts to meet quality objectives including the organizational structure and resources. Quality management, the fourth stage includes the first three and also the cost of quality. The hierarchy culminates with total quality management, which is management centered on quality, and aimed at long-term success through customer (patient, physician and payer) satisfaction. A number of quality control and quality assurance measures for cytopathology have been specified by the Clinical Laboratory Improvement Amendments of 1988. All QC and QA processes must be described and documented in the laboratory. **Pre-analytical Quality Control:** Each laboratory must perform and maintain records of routine quality control relating to specimen collection, receipt and preparation. Most of these activities are required by lab accreditation agencies and include such things as: Preparation and distribution of clinical specimen collection and handling instructions, Assurance of properly labeled specimens, Use of a requisition that provides space for all pertinent demographic and clinical data, Accessioning and assignment of a unique specimen identifier, Criteria for specimen rejection, Review of stain quality and maintenance of stain quality records, Procedure for preventing nongynecological specimen cross contamination, Microscope and instrument maintenance, Instrument calibration records.

Analytical Quality Control: Screening of Nongynecological Cytology Specimens: Federal regulations require that the individual examining a cytology specimen be a qualified cytotechnologist or pathologist in a certified laboratory. These individuals may examine up to 100 slides (gynecological and nongynecological) per 24 hours (average 12.5 slides/ hour) and in not less than eight hours. This number is not a performance target but a maximum allowed by law. Pathologists are limited by this ceiling when they perform primary screening. This includes nongynecological slides that have not been previously screened. Each laboratory must establish individual workload limits for each cytotechnologist. The Technical Supervisor of the laboratory must review these limits every six months and re-assess using lab defined performance standards. The record of slides reviewed by the primary screening cytotechnologist or pathologist must be documented and retrievable for inspectors during the retention period as prescribed. Cytotechnologists and pathologists must also maintain work logs for any primary screening site (in cases of multiple site employment), again, for the applicable retention period. As discussed later, all specimens must be reported using descriptive nomenclature; use of a numerical reporting system alone is unacceptable. **Review and Reporting of Nongynecological Cases:** All nongynecological specimens must be referred to a pathologist for final interpretation and final report. Discordance between pathologist and cytotechnologist interpretation, if the cases are screened prior to pathologist examination, can be used as a basis for identifying areas for continuing education. Peer review is often included in a quality assurance program. Multiple people may review difficult or interesting cases for educational and interpretive purposes. Laboratories may require a second pathologist opinion for specific diagnoses and/or type of specimen. See below for variability of documenting intralaboratory consultations. Seeking the opinion of an outside consultant may be considered for unusually difficult cases with significant clinical implications. Documentation of all reviews is essential for quality assurance monitoring. **Rescreening of Negative Cases:** Quality control rescreening of nongynecological cases is usually not required by accreditation agencies. However, re-examination of a subset of cases by a second pathologist prior to release of the final report may be incorporated into the anatomic pathology quality assurance program. The re-examined cases may be randomly chosen or may be selected based on volume and complexity of workload and cytopathology resources.

Post-analytical Quality Control: Cytological-Histological Correlation and Clinical Follow Up: The laboratory must make an effort to correlate nongynecological cytopathology findings with histology and clinical findings. This can be for all specimens or for a focused subset of specimens. It is suggested that if significant disparities exist they should be reconciled. Cytological-histological correlation can be an educational tool used to refine methods of evaluation for both cytology and tissue specimens. The correlation process should be documented in the laboratory quality assurance program. If a nongynecological cytology specimen is collected concurrently with a tissue specimen, cytological-histological correlation is best performed prospectively. Ideally, the cytology and tissue reports should each refer to the other with integration of the correlation statement into either report. Reporting cytological-histological discordance may be helpful in directing further patient management. If an abnormal or nondiagnostic nongynecological cytology result is subsequently followed with tissue sampling, and retrospective correlation is performed, then the result of the correlation should be documented. If histological material is not available, the laboratory may attempt to obtain patient follow-up by sending a letter to the ordering physician requesting this information. **Retrospective Reviews:** There are no federal or accrediting agency requirements for retrospective review of nongynecological cytology specimens. In certain clinical situations, review of previously examined specimens may affect current patient care by determining subsequent management protocols. Retrospective comparison of specimens from multiple body sites within a relatively short time span may be required for clinical staging, or comparison of a current specimen with one from the remote past may distinguish a metastasis from a second primary neoplasm. Amended reports are not indicated in these situations. Results of the review can be incorporated in the current cytology or tissue report or in a separate document. Retrospective reviews are subject to the biasing effect of knowledge of outcome, and this fact should be kept in mind during any such review. **Measures of Performance:** Nongynecological cytology can be both a screening test and a diagnostic procedure depending upon the clinical circumstances and specimen examined. Nongynecological cytology is limited (as are all laboratory tests) by both false positive (FP) and false negative (FN) results. As a screening test, a false positive is defined as a "positive" test result for a patient who does not have an abnormality. As a diagnostic procedure, a false positive could be defined as a malignant interpretation when in fact the patient has a benign neoplasm or perhaps as the presence of any neoplasm when the condition is reactive or inflammatory. Since "positive" results are variably defined in the medical literature, a standard definition for a false positive nongynecological cytology specimen does not exist. A false negative is defined in this document as a negative or nondiagnostic nongynecological cytology result in a patient with an abnormality or lesion. False negative results may be a consequence of (a.) Sampling variance, (b.) Laboratory interpretation, or (c.) General limitations of the method. Sampling false-negatives occur when diagnostic cellular and noncellular material is not collected or is not transferred to the slide. A laboratory interpretive false negative is one in which diagnostic material is present on the slide, but is not identified during slide examination or is misinterpreted as to its significance. The false negative rate is the sum of lesions missed in sampling plus the false negative proportion (FNP.) The FNP is the measure of the laboratory component of false negative results and is defined as the number of false negative reports divided by the total number of patients sampled who have an abnormality (False Negative Proportion = False Negative reports/True Positive reports + False Negative reports). FNP = FN/TP + FN. The value of determining the FNP for a laboratory is widely acknowledged; however, precise calculation of the FNP requires 100% accurate determination of the true diagnosis. For nongynecological cytology this requires exhaustive cyto-histologic and clinical correlation, which is impractical. Q-Probes studies provide a comprehensive resource for comparative laboratory data and performance benchmarks. These data are a good starting point for laboratory self-assessment since operational definitions, laboratory methods and statistical analyses are specified.

TULIP NEWS

The minimum clotting time of whole blood is 20-30 minutes

Coral Introduces

FASTRAK®

THROMBIN REAGENT

Clots blood in 1 min !!

The normal clotting time can be reduced using FASTRAK®.
Leads to increased work efficiency and improved patient management.

Improving "Pre-analyticals"

Printed and published by D.G. Tripathi, Edited by Dr. Ramnik Sood, M.D. (Path.) for and on behalf of Tulip Diagnostics Private Ltd., Gitanjali, Tulip Block, Dr. Antonio Do Rego Bagh, Alto Santacruz, Bambolim Complex Post Office, Goa - 403 202, INDIA.
Fax: (0832) 2458544. E-mail: sales@tulipgroup.com Website: www.tulipgroup.com