Anatomy and pathophysiology of gout and lupus

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Introduction

Gout is an acute inflammatory arthritis with the potency to fully destroy the integrity of the joint leading to severe disability. It is termed as a “ true crystal deposition disease” caused by formation of monosodium urate crystals in joints and other tissues. It is the common cause of inflammatory arthritis that has increased in prevalence in recent decades (Roddy and Doherty 2010). Gout normally results from the interaction of genetic, constitutional and environmental risk factors. It is more common in men and strongly age related. Both acute arthritis and chronic arthropathy (tophaceous gout) are considered under the rubric of gout (Mikuls and Saag 2006; Roddy et al. 2007). In a broader term, it can be defined as combination of events involving an increase in the serum urate concentration, acute arthritic attacks with monosodium urate monohydrate crystals demonstrable in synovial fluid leukocytes, and tophi which usually occurs in and around joints of the extremities. These physio-chemical changes either occur separately or in combination (Terkeltaub 2003; Shai et al. 2010). Gouty arthritis accounts for millions of outpatient visits annually and the prevalence is rising. It affects 1-2% of adults in developed countries, where it is the most common inflammatory arthritis in men. Epidemiological data are consistent with a rise in prevalence of gout. Rates of gout have approximately doubled between 1990 and 2010. A number of factors have been found to influence rates of gout, including age, race, and the season of the year. In men over the age of 30 and women over the age of 50, prevalence is 2% (Eggebeen 2007).

Anatomy and Pathophysiology

Gouty arthritis is one of the most painful rheumatic diseases and its incidence increases promptly with advancing age. In 75% of the patients, gouty arthritis initially strikes a single joint which is most commonly the big toe. In women gout develop in increasing numbers after menopause eventually at an incidence rate equal to that of men (Hootman and Helmick 2006). In elderly patients, an occurrence of gout is usually less spectacular than in middle age and often implies an upper extremity poly or mono articular presentation rather than the classic mono articular lower extremity picture commonly displayed by middle-aged men. In older patients, gout can be more likely the clinical picture of osteoarthritis or rheumatoid arthritis (Cassetta and Gorevic 2004). Gouty arthritis can be classified into four stages depending upon level of severity namely; (i) Asymptomatic Hyperuricemia: In this stage, a person has elevated blood uric acid levels but no other symptoms and therefore requires no treatment. (ii) Acute Gouty Arthritis: In this stage, hyperuricemia leads to deposition of uric acid crystals in joint spaces, leading to gouty attacks (iii) Interval / Intercritical: This is the stage between acute gouty attacks with no symptoms and (iv) Chronic Tophaceous Gout: where the disease leads to permanent damage (Bhansing et al. 2010).

Pathogenesis of gouty arthritis is critically influenced by sodium urate crystals and inflammatory processes they induce (Wise and Agudelo 1996). An inefficient renal urate excretion which leads to the elevated levels of uric acid above the saturation point for urate crystal formation is a major determinant of the disease. Purine catabolism leads to the formation of

metabolic by-product, uric acid. In most mammals like higher primates, many birds and some reptiles, the urate oxidase (uricase) enzyme converts uric acid (relatively insoluble) to allantoin (highly soluble), leading to very low serum uric acid levels. A series of parallel mutations in the genes of uricase in the Miocene period results in the production of the dysfunctional form of uricase that leads to accumulation of relatively higher level of insoluble uric acid and subsequently the development of gouty arthritis (Liote and Ea 2006; Eggebeen 2007). Degradation of purines results in the endogenous production of uric acid that usually contributes about two-thirds of the body urate pool, the remainder being originated by dietry intake. Of the uric acid formed daily, about 70% is excreted through the kidney while the rest is eliminated into the biliary tract and then converted to allantoin by colonic bacterial uricase. Therefore, in the vast majority gouty patients, hyperuricaemia occurs from reduced efficiency of renal urate clearance (Laubscher et al. 2009; Terkeltaub 2010).

Development of the acute and chronic inflammatory gout is facilitated with the deposition of monosodium urate (MSU) crystals in joints. while MSU crystals were first identified as the aetiological agent of gout in the eighteenth century and more recently as a ‘ danger signal’ released from dying cells, little is known about the molecular mechanisms underlying MSU-induced inflammation (Martinon et al. 2006). For crystal formation n occurrence of gout, the ionic product of sodium and uric acid must be at or above the saturation level at which MSU crystals can form. Uric acid is a weak acid of pKa 5. 75 and, it exists mainly in the ionized form as urate at physiological pH of 7. 40. MSU has limited solubility under physiological

conditions and the saturation level in plasma at a pH of 7. 40 is 6. 8 mg/dl (408 µmol/l) and when the plasma concentration exceeds this level, crystals may form in the joints and tissues (Terkeltaub 2010).

MSU crystals preferentially form within cartilage and fibrous tissues, where they are relatively safer from contact with inflammatory mediators and may dwell for years without causing any defects. However, if ‘ shed’ from these sites of origin into the joint space or bursa, they are highly phlogistic particles that are immediately phagocytosed by monocytes and macrophages, stimulating the NALP3 inflammasome, triggering the release of IL-1 and other cytokines and a subsequent infiltration of neutrophils. Here the white cells release a package of inflammatory mediator substances which, in addition to destroying the crystals, also damage the surrounding tissues (Martinon et al. 2006). This acute inflammation defines the symptoms of an acute flare such as pain, swelling and redness and is typically self-limiting. Continual deposition of large numbers of MSU crystals may also heading out the joint damage through mechanical effects on cartilage and bone (pressure erosion), and probably low-grade inflammation. However, these more chronic crystal-tissue interactions still remain elusive and in need of further investigations (VanItallie 2010).

Systematic Lupus Erythematosus (SLE)

Introduction

Lupus is an autoimmune disease which leads to both acute and chronic inflammation of various tissues of the human body. Lupus can be classified into different form depending upon the target tissues and organ system. Defined as Type III hypersensitivity reaction, people with lupus produce

abnormal antibodies in their blood that target tissues within their own body rather than foreign infectious agents. Because the antibodies and accompanying cells of inflammation can affect tissues anywhere in the body, lupus has the potential to affect a variety of areas such as heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. When internal organs are involved, the condition is referred to as systemic lupus erythematosus (SLE). The disease may be mild or severe and life-threatening (Wallace 2010).

The prevalence of lupus ranges from approximately 40 cases per 100, 000 persons among Northern Europeans to more than 200 per 100, 000 persons among blacks (Johnson et al. 1995). In the United States, the number of patients with lupus exceeds 250, 000. The life expectancy of such patients has improved from an approximate 4-year survival rate of 50% in the 1950s to a 15-year survival rate of 80% today (Merrell and Shulman 1955; Abu-Shakra et al. 1995). Even so, a patient in whom lupus is diagnosed at 20 years of age still has a 1 in 6 chance of dying by 35 years of age, most often from lupus or infection. Later, myocardial infarction and stroke become important causes of death (Cervera et al. 2003).

Anatomy and Pathophysiology

SLE is an inflammatory and multi-systemic autoimmune disorder characterized by an uncontrolled auto-reactivity of B and T lymphocytes. This results in the production of auto antibodies (auto-Abs) against self-directed antigens and causes tissue destruction (Cuchacovich and Gedalia 2009). Pathogenesis of SLE is a multi-factorial event and the exact mechanism of disease development and progression is still unclear. Multiple

factors are known to be associated with the development of the disease such as genetic, racial, hormonal, and environmental factors.

Defects in apoptosis are one of the proposed mechanisms involved in patho-physiological events of SLE. Imbalance in apoptotic machinery leads to the production of auto-antibodies. These antibodies lack the ability to differentiate between pathogenic and normal host cells and cause increase cell death and abnormalities in immune tolerance (Andrade et al. 2000; Rahman and Isenberg 2008). It is believed that all the major components of immune system are involved in SLE progression at various levels. Mostly proteins present in cell nucleus are targeted by the immune system. The likely environmental triggers for SLE include ultraviolet light, drugs, and viruses. These stimuli cause the destruction of cells and expose their DNA, histones, and other proteins, particularly parts of the cell nucleus. It is observed that in patients suffering from SLE, there is increased cell death in monocytes and keratinocytes and hyper expression of Fas protein by B and T cells of the immune system. Tingible body macrophages (TBMs) are large phagocytic cells present in the germinal centers of secondary lymph nodes. They express CD68 protein. These cells normally engulf B cells which have undergone apoptosis after somatic hypermutation. In some patients with SLE, significantly fewer TBMs can be found, and these cells rarely contain material from apoptotic B cells. Also, uningested apoptotic nuclei can be found outside of TBMs. This material may present a threat to the tolerization of B cells and T cells (Gaipl et al. 2006).

Monocytes isolated from whole blood of SLE sufferers show reduced expression of CD44 surface molecules involved in the uptake of apoptotic

cells. Most of the monocytes and tingible body macrophages (TBM), which are found in the germinal centres of lymph nodes, even show a definitely different morphology; they are smaller or scarce and die earlier. Serum components like complement factors, CRP, and some glycoproteins are, furthermore, decisively important for an efficiently operating phagocytosis. With SLE, these components are often missing, diminished, or inefficient.

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