Interdepartmental Conference

Drug-Induced Stevens-Johnson Syndrome

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Abstract : **A patient with arthritis receiving allopurinol for 4 weeks developed Stevens-Johnson syndrome (SJS). SJS is a potentially life-threatening adverse drug reaction and is most commonly associated with the sulfa antibiotics, allopurinol, NSAIDs, and anticonvulsants. The skin reaction spread symmetrically over the body and involved the conjunctiva. The diagnosis and different models of treatment for this case are discussed. Alternative treatments for gouty arthritis are presented. Strategic planning for novel research opportunities arising from this disease is outlined.**

Key words : Stevens-Johnson syndrome, adverse drug reaction

เรื่องย่อ : **ผิวเปื่อยเพราะยา**

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ผู้ป่วยชื่อชักเสบหนึ่งรายได้รับยา allopurinol เป็นเวลา 4 สัปดาห์ แล้วเกิดฤทธิ์แทรกแซงแบบ Stevens-Johnson syndrome (SJS) กลุ่มอาการนี้มีการดำเนินของโรครุนแรงถึงชีวิตได้ และมักมีประวัติการบริหารยาในกลุ่ม sulfa antibiotics, allopurinol, NSAIDs หรือยากันชัก ผื่นผิวหนังที่ปรากฏพบมีกระจายสมดุลกันทั้งซ้ายและขวา รวมทั้งมีการอักเสบของเยื่อบุนัยน์ตา รายงานนี้ได้อภิปรายการวินิจฉัย แนวทางการรักษาสำหรับผู้ป่วยรายนี้ การเลือกยารักษาโรคไขข้อที่เหมาะสมมาแทนที่ allopurinol รวมทั้งการวางแผนทำวิจัยใหม่ ๆ สำหรับกลุ่มอาการนี้

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INTRODUCTION

Stevens-Johnson syndrome (SJS) is a type IV (delayed) hypersensitivity reaction that causes a serious and potentially fatal skin eruption. SJS and toxic epidermal necrolysis (TEN) share a common pathophysiology and histopathology. The lesions in SJS and TEN consist of irregular blisters and macules unevenly distributed over the entire face and body and involve at least one mucous membrane. Painful blisters develop in the mouth, eyes, and genital tract. TEN shows epidermal detachment (>30%) to a greater extent than SJS (<10%). The incidence of SJS is much higher in individual who are HIV seropositive, or who have HSV or mycoplasma than in the general population. SJS often has a prodromal phase with fever, cough, and malaise for a few days prior to the onset of cutaneous symptoms. An exposure period to the reactive agent or infection of approximately 1-3 weeks is usual before developing a skin eruption that is consistent with a cellular immune response. The skin eruption develops symmetrically over the entire body for 3-4 days starting as erythematous or purpuric macules followed by blistering and skin necrosis.

Identifying a causal relationship may be difficult in a situation in which multiple drugs and exposure to infection are present. The classes of drugs that often cause SJS are the sulfa antimicrobials and allopurinol. Other causative agents include anticonvulsants (phenobarbital, phenytoin, carbamazepine, valproic acid), lamotrigine, gabapentin, NSAIDs (tenoxicam, piroxicam, oxaprozin, diclofenac, sulindac, tiaprofenic acid), penicillins (amoxicillin, ampicillin, and piperacillin), macrolides (erythromycin), cephalosporins (cephalexin), fluoroquinolones (ciprofloxacin), glycopeptides (vancomycin), tetracyclines (doxycycline and minocycline), folate inhibitors (trimethoprim), nitrofurantoin, rifampin, ethambutol, streptomycin, antihypertensives (carvedilol and diltiazem), antiretroviral medications (nevirapine and didanosine), theophylline, pentoxifylline, methazolamide, and propylthiouracil.

CASE REPORT

A 46-year old Thai male was diagnosed with gouty arthritis 6 months ago, first presenting with a swelling over left foot. His treatment consisted of 1.2 mg colchicine, 1,200 mg ibuprofen, and 45 mL alum milk daily. All treatment was discontinued after his symptoms resolved. A month before admission, he developed a painful swelling over the right first toe. His plasma uric acid level was 10.2 mg/dL. He received 1.8 mg colchicine, 75 mg indomethacin daily. After a week of treatment, his symptoms resolved, and a daily regimen of 900 mg allopurinol and 1.2 mg colchicine was given. Five days before admission, he developed fever, myalgia and a bleb over the nape of his neck. Three days before admission, he developed a sore throat. Macula rashes spread over his torso. Blebs were found over the left side of his back. On the day before admission, both eyes developed conjunctivitis and diaphoresis. This was treated with 2 g amoxicillin and tobramycin eye drops. The skin rash and blebs were denser over his torso, neck, face and scalp. He was admitted for 10 days and received an 8-day course of steroids until clinically improved.

DISCUSSION

Dermatologic Aspect

When a patient has an acquired vesiculobullous eruption, the differential diagnosis includes drug eruptions, infections such as chickenpox and autoimmune vesiculobullous diseases. However, this patient had a fever, abnormal liver function test (hepatocellular type), a skin rash (vesicles), severe oral and ocular mucosal involvement, and also had target skin lesions which were characteristic for SJS so that the diagnosis was straightforward. Autoimmune vesiculobullous diseases do not usually have a fever unless there is a secondary infection, and usually have a longer history of skin lesions present intermittently. Chickenpox usually has vesicles that turn rapidly (within one to two days) to pustules and usually has no severe mucosal involvement.

Drugs are the major etiologic factors in SJS. In the minority of cases, infectious agents such as Mycoplasma pneumoniae[1] etc. are responsible. From the sensitization period, the suspected culprit drugs in our case are allopurinol, colchicine, and indomethacin. However, cutaneous reaction to colchicine and indomethacin are infrequent[2]. The most likely

etiologic agent in this case was allopurinol.

Allopurinol is generally well tolerated. Approximately 2% of patients taking this drug develop a mild cutaneous rash. Allopurinol hypersensitivity syndrome (AHS) is an infrequent but life-threatening adverse reaction. The exact mechanism responsible is unknown. Three mechanisms that may be involved are immunologic factors (a type III or type IV reaction), genetic predisposition, and accumulation of the drug especially in patients with poor renal function.

Table 1 shows Singer and Wallace's diagnostic criteria for AHS[3]. Our patient had a 3-week history of allopurinol intake, acute hepatocellular injury, erythema multiforme major (SJS) and fever. However, we could not absolutely exclude the possibility of reaction to colchicine and indomethacin. Rechallenge to confirm which drug is responsible to the disease is contraindicated in a severe drug reaction. So we limited the diagnosis of our patient to SJS.

Treatment of SJS has to be individually tailored according to cause, stage and presence and type of complication. Systemic corticosteroids should not be used routinely but only under special circumstances and with caution. They may be used in the very early stages of drug-induced SJS (and TEN) in relatively high doses for a short period. The dosage should be stopped or tapered quickly as the disease stops progressing. Treatment must focus on early detection and prevention of complications. Supportive care is of great importance. Debridement of necrotic skin should not be performed before disease activity ceases.

There are pros and cons to using corticosteroids in the treatment of SJS and toxic epidermal necrolysis (TEN)[4]. The following claims have been made against the use of corticosteroids: 1) patients treated with systemic corticosteroids have a poorer prognosis than those treated without; 2) corticosteroids further impair the patients' immune response, increasing the risk of severe infection; 3) TEN may develop in patients who are already being treated with high dose corticosteroids for another underlying disease.

Against these claims are: 1) controlled studies[5] and clinical experiences have shown that corticosteroids do influence the development of lesions; 2) mortality rates are very different in patients series; 3) corticosteroids limit the extent and depth of skin and mucosal necrosis and reduce the severity of sequelae.

Alternative systemic treatment include plasmapheresis[6], cyclophosphamide[7], pentoxifylline[8], intravenous immunoglobulin[9], intravenous ulinastatin[10].

The mortality rate of SJS depends on the severity of the disease and the quality of medical care. It may be as low as 1%[11] or in untreated case may be as high as 5 to 15%. It may take between 3 to 6 weeks to clear. There is a tendency for scar and stricture formation at the mucosal sites.

Ophthalmologic Aspect

On admission, the patient had epiphora, mild lid edema, red eye and a profuse mucous discharge for one day after SJS had been present for 5 days. Although the symptoms and signs in this patient were of mild severity which might resolve spontaneously without sequelae unless secondary bacterial infection occurred. He was prescribed topical antibiotic eye drop every hour for two days which could increase the risk of corneal epithelial damage and punctate epitheliopathy as a result of preservative toxicity. As we know, all topical eye preparation always contain preservative. Moreover, this patient with conjunctivitis was given topical antibiotic eye drops (ciprofloxacin) of unnecessary high potency during and after admission. It should be reserved for corneal ulcer only because of the risk of rapid and high drug resistance. Furthermore, topical corticosteroids were instilled for a long period (more than a month). Therefore, the patient had a greater risk of side effects such as steroid induced glaucoma or superimposed infection.

The acute phase of eye disease in SJS usually persists for 2-6 weeks, but conjunctival injection in this patient decreased within a week. The eyelids were swollen, erythematous, encrusted, with frank ulcer and loss of eyelashes. The conjunctiva was hyperemic with distinct vesicles or bullae. Ocular manifestations in all erythema multiforme cases are found in 24%, especially in Stevens – Johnson syndrome (69%), toxic epidermal necrolysis (50%)

Table 1. Singer and Wallace's diagnostic criteria for allopurinol hypersensitivity syndrome (AHS).

1. A clear history of exposure to allopurinol
2. A clinical picture consisting of either A or B

A. At least two of the following criteria
   1. Worsening renal function
   2. Acute hepatocellular injury
   3. A rash including either TEN, erythema multiforme, or a diffuse maculopapular or exfoliative dermatitis

B. One of the above major criteria plus at least one of the following minor criteria
   1. Fever (> 37.5°C)
   2. Eosinophilia (absolute eosinophil count > 0.5×10^9/L)
   3. Leukocytosis (normal range $3.0 - 10.0 \times 10^9$/L)
   4. Lack of exposure to any drug that may cause a similar clinical picture

* All three of these criteria need to be present

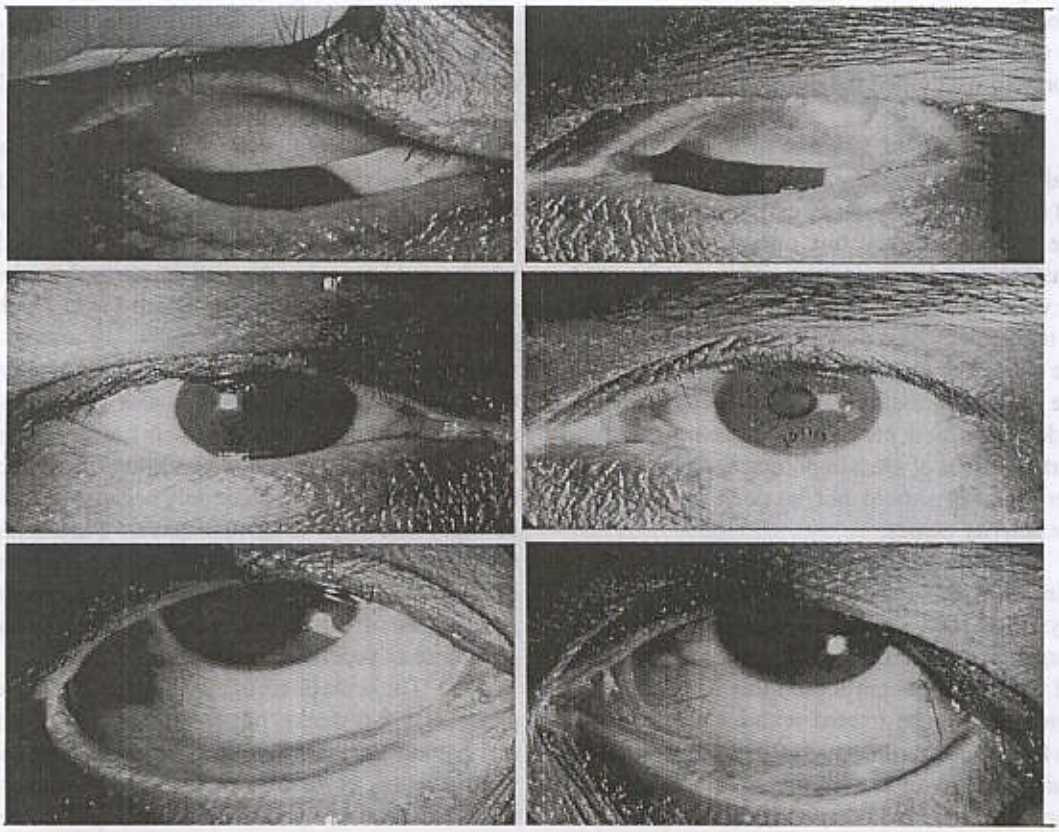

Figure 1. Two months after SJS : no injection, minimal irritation sometimes, comfort without feeling of dry eye, mild symblepharon of the right lower lid (nasal) and left lower lid (temporal and nasal), and some palpebral scar of the left upper lid. Visual acuity was 6/6 both eyes. Intraocular pressure in the right eye was 10.5 mmHg, left eye 13 mmHg.

and erythema multiforme minor (9%). However, there is no significant difference in eye findings with or without systemic steroids[12]. Most symptoms and signs are mild (54%), moderate (19%) and severe involvement occurs in 27%. Pseudomembranous or membranous conjunctivitis at the epithelial surface of tarsal and bulbar conjunctiva, and coalescence of fibrin with necrotic cellular debris is graded as moderate severity. Cicatricial conjunctivitis with corneal epithelial loss of over 30% is found in 43%, and corneal ulcers in 5% of those with moderately severe ocular involvement. Recurrent episodes tend to have limited complications. In severe cases, corneal vesicle, corneal melt and perforation may occur with inflammation, reduced vision, conjunctival fornix foreshortening and symblepharon.

Late phase complication are found in 20%, consisting of scarring of the lids and conjunctiva, malposition of the eyelid manifesting as ectropion, resulting in corneal exposure and punctate epithelial keratitis, and entropion or trichiasis causing corneal abrasion.

Chronic inflammation of the tarsal conjunctiva leads to keratinization of the palpebral conjunctiva adjacent to the eyelid margin. Symblepharon increases the risk of infection, punctate epithelial keratitis, and corneal exposure from incomplete blinking. Lagophthalmos caused by poor eyelid closure from scarring of the upper lid, results in incomplete blinking induced corneal exposure, punctate epithelial keratitis, poor removal of tear film debris, recurrent corneal epithelial defects, infection, scarring, neovascularization and opacity. Tear deficiency is the latest complication of SJS, as a result of keratoconjunctivitis sicca arising from scarring of the lacrimal duct orifices and mucin deficiency from destruction of the conjunctival goblet cells. Alteration in the mechanical function of lids, dry eye and breakdown of the corneal epithelium lead to corneal ulcer, perforation, panophthalmitis and blindness. Therefore prompt ophthalmic consultation should be considered in all patients with ocular involvement. Early proper management is the most important approach to minimize morbidity and blindness. This includes frequent irrigation with preservative-free artificial tear and inspection of the superior and inferior fornices and daily debridement under topical anesthesia.

Rheumatologic Aspect

Hyperuricemia is a common problems in general practice. Approximately 5-8% of the general population and up to 15% of hospitalized patients have an elevated serum urate level[13]. The prevalence of hyperuricemia in Asia has been reported to be up to 30-40%[14,15], which is higher than that in European countries[16]. Despite its high prevalence, most patients with hyperuricemia are asymptomatic while less than 20-30% have symptoms of gouty arthritis and nephrolithiasis[17]. The urate-lowing agents are indicated only in those with symptomatic hyperuricemia[17].

Gouty arthritis is the commonest form of inflammatory arthritis in men over the age of 40. Its incidence varies between 1 to 15 in 1,000[18]. It occurs mainly in patients with chronic, long-standing hyperuricemia. However, hyperuricemia is not essentially required for the diagnosis of acute gouty arthritis. The definitive diagnosis of gout should be established by demonstration of intracellular monosodium urate crystals in the synovial fluid of an affected joint. In the absence of crystal identification, the following combination of findings may be useful in suggesting a diagnosis of gout[17,18].

Acute monoarthritis commonly located in the first metatarsophalangeal joint or the ankle is the main presenting feature of gouty arthritis[17,18]. Tendinitis and extraarticular inflammation may occur but usually present in those with multiple, recurrent attacks particularly in the stage of chronic tophaceous gout[17,18]. Six months before admission, this patient had an acute, painful swelling of left plantar area which might have been an acute plantar fasciitis or other soft tissue inflammation. According to the diagnostic criteria described previously, the diagnosis of gout should not have been made at that time, although the serum urate level was high. Five months later, he had an episode of suspected arthritis of the right first toe while urate level was elevated. Since this attack resolved with colchicine treatment, the diagnosis of gouty arthritis would be appropriate at this point.

Colchicine is the most effective primary therapy in gout. Nonsteroidal antiinflammatory agent (NSAID) can be used alternatively or in addition to colchicine[17,18]. NSAIDs are very effective in

controlling pain and inflammation but their potential side effects should be considered especially gastrointestinal (GI) problems[19,20]. The established risk factors for NSAID-induced GI adverse events include advanced age, previous history of peptic ulcer, coadministration of steroids, high dose or multiple use of NSAIDs, and serious systemic disorders[20].

This patient should be categorized in the high risk group because he had a 5-year history of duodenal ulcer with a bout of ulcer bleeding. In this setting, NSAID use should be avoided as much as possible. If it remains indicated, coadministration with omeprazole or misoprostol has been shown to be cost-effective for prophylaxis of NSAID-induced GI adverse events. However, this patient received ibuprofen/indomethacin in addition to colchicine treatment without any GI prophylaxis.

Allopurinol is a urate-lowering agent frequently used in everyday practice. Generally, 200 to 300 milligrams are adequate for the control of hyperuricemia[21]. A dosage higher than 400 mg is rarely required. A higher dose of allopurinol has been reported to be associated with hypersensitivity syndrome, due to the higher level of its active, long-acting metabolite oxypurinol[22]. A 600-mg dosage may have resulted in the allopurinol hypersensitivity syndrome in this case. Since he had a severe reaction to allopurinol, re-challenge with this agent should be avoided[22]. The alternative choice to control hyperuricemia is the uricosuric agent such as probenecid or benzbromarone[17,18].

Pharmacokinetic Aspect

It is generally held that the severity of Stevens-Johnson syndrome does not correlate with drug dosage, plasma drug level and drug elimination half-life. However, patients with prolonged acylation of sulfonamide that shift the metabolism to hydroxylamine via an alternative oxidative pathway are more likely to develop the disease and more likely to have severe disease. SJS is also frequently associated with viral infection that increases drug metabolism into metabolites[23] as reported at the start of the HIV epidemic[24]. Viral infections were proposed to induce non-specific polyclonal activation of $CD8^+$ T cells and drug-specific T cells[25]. These findings imply that the disease episode may correlate with the plasma level of sensitized drug. The potentially fatal nature of the disease has precluded the possibility of challenging the patients with a graded dosage of sensitized drugs. However, prick tests and intradermal tests have been studied and have usually yielded negative results[26]. Prolonged elevation of sensitized drug in plasma as a result of giving a high dosage of drug or drug interaction is usually accompanied by more frequent and more severe drug reactions. It is possible to investigate the plasma concentration-response and exposure time-response relationships using an in vitro cytotoxic assay employing isolated peripheral blood mononuclear cells or purified $CD8^+$ T cells as effector cells and autologous cultured keratinocytes as target cells. The clear identification of the responsible drugs using clinical or biological tests has yet to be established[27].

Pharmacodynamic (immunologic) Aspects

Stevens-Johnson syndrome and toxic epidermal necrolysis share a common pathophysiology and histopathological findings[27]. The reactions are characterized by cytolysis or apoptosis of keratinocytes[28] mediated by $CD8^+$ T cells invading the epidermis, and local cytokine release. The immunological mechanism is similar to the graft-versus-host reaction[25,27]. The cytolysis has been proposed to be mediated by several mechanisms, i.e. $CD8^+$ T cell cytotoxicity, tumor necrosis factor-α release, and direct drug toxicity. $CD8^+$ T cells and macrophages are present over the epidermis while $CD4^+$ T cells are present over the upper dermis. Keratinocytes abnormally express HLA class II and adhesion molecules (ICAM 1).

The activation of $CD8^+$ T cells generally requires the presentation of antigenic oligopeptide of HLA class II on the surface of antigen-presenting cells (APC). In this case, keratinocytes act as antigen-presenting cells. The involvement of superantigens in the pathogenesis as proposed in atopic dermatitis and psoriasis is precluded due to the prerequisite of the long (up to 1 month or more) sensitization period. It is commonly held that the immune system is sensitized against the active drug, but the exact epitope whether it is on the active drug, metabolites, or drug haptens has not yet been identified. The

elution of sensitized epitope from the HLA class II complex on isolated keratinocytes pulsed with sensitized drug should provide information toward identifying the epitope. Some HLA phenotypes (HLA A29, HLA B12, HLA DR7) have been associated with the risk of sulfonamide-induced toxic epidermal necroly-sis[29,30]. A selective expression of TCR Vβ17$^+$ has been found on CD4$^+$ and CD8$^+$ T cells from an allergic subject following 9-day exposure to sulfamethoxa-zole in vitro[31] suggesting that drug-specific T cells displayed a limited TCR usage.

SJS does not involve all skin regions evenly; the scalp is usually spared from the disease[27]. Since apoptosis has been proposed to be one of the most important mechanisms of keratinocyte lysis[28], TNF-α, granzyme B, perforin[32,33], IL-12, interferon-γ, Fas ligand and nitric oxide synthase have been detected and proposed as causative agents[34,35]. The role of other molecules of the tumor necrosis factor family (e.g., TRAIL ligand, CD40 ligand) deserve similar investigative strategies.

There has been no attempt to unequivocally identify the Stevens-Johnson syndrome-inducing drugs that closely simulate a physiological setting. Increased IFN-γ release has been observed following an in vitro challenge of a patient lymphocytes with allopurinol without any involvement of keratinocyte[36]. Keratinocytes from sulfamethoxazole-reactive patient were specifically killed predominantly by CD4$^+$ T-cell clones only after pretreatment of the keratinocytes with IFN-γ[33]. Challenge or desensitization with the allegedly sensitized drugs is unethical in this syndrome. To circumvent the in vivo test, an alternative in vitro reconstitution system of cytotoxic assay can be applied employing isolated peripheral blood mononuclear cells or purified CD8$^+$ T cells as effector cells and autologous cultured keratinocytes pre-sensitized with putative drugs as target cells.

Comment

Stevens-Johnson syndrome is one of the most severe mucocutaneous adverse drug reactions which can result in either morbidity or mortality. It is rarely found in normal people and its incidence can be reduced by starting with a low dose of the drug known to be the cause of this syndrome and increasing the dose slowly. Immune tolerance probably plays an important role in the absence of this syndrome in most people and the lowered incidence when the dose has been stepped up slowly. Starting with the full maintenance dose of the drug places the patient at risk of developing this syndrome. If the mechanisms of immune tolerance are disentangled, screening test to detect individuals with absent or low level of immune tolerance can be developed to help detect individual at risk of developing this syndrome.

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