Case Report

Allopurinol induced SJS

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OUTLINE

- 案例報告
- 疾病介紹
- 國外文獻回顧
- 國內統計資料
- 總結

Case report

病人基本資料(1)

- 性別: 女
- 年齡: 73歲
- 入院日期: 2013/7/20
- 病患主訴:
  - Intermittent conscious loss recently
- 入院診斷:
  - Fever
  - Diabetes with renal manifestations
  - Urinary tract infection (UTI)
  - Hypokalemia
  - Snycope, r/o seizure, r/o electrolytes imbalance or infection related, or intracranial lesion related

病人基本資料(2)

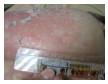
- 過往病史:
  - Cellulitis, lip, suspect herpetic labialis
  - Oral candidiasis, improved
  - Type 2 DM
  - Hypertension
  - CKD
  - Chronic ischemic heart disease
  - Parkinsonism
- 過敏紀錄: Nil
- 家族病史: Nil

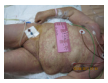
不良反應進程(1)

- 2013/7/5
  - 全身紅疹曾於皮膚科門診就醫，使用口服Fexofenadine 60 mg BID
- 2013/7/19
  - 仍有紅疹，再次於皮膚科門診就醫，加開Fluocinonide藥膏
- 2013/7/20
  - 因UTI及發燒住院，給予抗生素Ceftazidime 1g IV QD治療，同時有服用多種自備藥品
- 2013/7/21
  - 仍全身紅疹，值班醫師開立Chlorpheniramine 5 mg IV ST+Q12H，並DC自備藥品Allopurinol

不良反應進程(2)

- 2013/7/22
  - DC其他自備藥品
- 2013/7/25
  - 身上仍有紅疹，會診皮膚科，診斷為疑似Allopurinol 引起Steven's Johnson syndrome ，使用外用藥Menphencala BID、Fucidin(傷口) BID
- 2013/7/27
  - 給予Hydrocortisone 200 mg IV Q6H
- 2013/8/2
  - 解大量血便且意識改變，轉至ICU治療
- 2013/8/5
  - 皮膚紅疹改善，顏色變深





檢驗數據

檢驗項目	單位	6/10	7/19	7/20	7/22	7/23	7/26	7/29	8/1	8/2
BUN	mg/dL		21			32	26	43	33	33
CREA	mg/dL	0.91	1.41	1.89	1.82	1.88	1.57	2.15	1.58	2.04
eGFR	ml/min/1.73m^3	>60	38.9	27.7	28.9	27.9	34.3	23.9	34.1	25.4
Na	mmol/L	140	130	131	137	138	135	144	151	152
K	mmol/L	3.3	2.6	2.77	2.3	2.4	3.7	2.9	2.8	4.1
CRP定量	mg/dL	24.83	6.79	9.75			12.32			
AST	U/L			17			53			
ALT	U/L	4					39			
WBC	10^3/ul	4.7	9.32	8.63		11.09	14.17	18.79	17.8	19.24
RBC	10^3/ul	3.77	3.82	3.93						
Hb	g/dL	11.7	12.1	12.7		12.2	12.4	11.2	12.9	8.5
Platelet	10^3/ul	183	209	168		196	184	236	262	236
NEU	%	46.2	57.8	69.7		54	38.1	63.7	57.8	65.5
LYM	%	28.9	12.9	10.2		10	29.6	29	30.2	31.8
MONO	%	20.9	7.1	9.4		11	9.2	4.4	5.2	2.3
EOS	%	2.3	21.2	9.3		25	20.3	1.6	6.1	0.2
BASO	%	1.7	1	1.4		0	2.8	1.3	0.7	0.2
TLC	cells/mu	1358.3	1202.3	880.3		1109	4194.3	5449.1	5375.6	6118.3

造成不良反應疑似藥品

- Allopurinol
  - 已知的使用記錄
    - ✓102/3/26~102/4/10
    - ✓102/7/2~102/7/21
  - 會診皮膚科的診斷結果
  - 通報案例多
- Nateglinide
  - 已知的使用記錄
    - ✓102/7/2~102/8/2
  - 新加入使用的藥品

Stevens-Johnson syndrome

Epidemiology

- Estimates of incidence for all three disorders per million people per year
- SJS : TEN = 3 : 1
- Can occur in patients of any age
- Women account for over 60 percent of cases

Etiologies

- In adults
  - Medications cause 30 to 50 percent of cases of SJS and up to 80 percent of cases of TEN
  - Infections are the next most common trigger of adult SJS (up to 15 percent)
  - Medications
    - ✓ Anti-gout agents (especially allopurinol)
    - ✓ Antibiotics (sulfonamides >> penicillins > cephalosporins)
    - ✓ Antipsychotics and anti-epileptics (including carbamazepine, dilantin, lamotrigine, and phenobarbital)
    - ✓ Analgesics and non-steroidal anti-inflammatory agents (especially piroxicam)
- In children
  - Medications are the leading cause of SJS and TEN
  - Infections, particularly mycoplasma pneumonia and herpes viruses, are associated with a greater proportion

Clinical presentation(1)

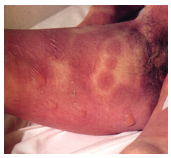
- Prodrome
  - Fever and influenza-like symptoms one to three days before the development of mucocutaneous lesions
  - Fever is usually higher with TEN, and often exceeds 39 degrees Celsius
  - Alert clinicians to the possibility of SJS/TEN
    - ✓ Confluent erythema (erythroderma)
    - ✓ Facial edema or central facial involvement
    - ✓ Skin pain
    - ✓ Palpable purpura
    - ✓ Skin necrosis
    - ✓ Blisters and/or epidermal detachment
    - ✓ Mucous membrane erosions and crusting
    - ✓ Swelling of tongue

Clinical presentation(2)

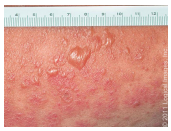
- Skin
  - A burning sensation or other paresthesias may be noted
  - Lesions are symmetrically distributed, and start upon the face and thorax before spreading to other areas
  - Vesicles and bullae then form and the skin begins to slough within days
- Mucosa
  - Mucous membranes are involved in more than 90 percent of cases of SJS/TEN
  - Typically, at least two mucus membranes are affected

Clinical presentation(3)

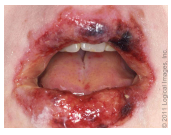
- Laboratory abnormalities
  - Hematologic abnormalities, particularly anemia and lymphopenia, are common in TEN
  - Eosinophilia is unusual, despite the strong association of TEN with drug ingestion
  - Neutropenia is noted in about one-third of patients, and is correlated with a poor prognosis
- Time course
  - From prodrome to hospital discharge in the absence of significant complications, is typically two to four weeks
- Reepithelialization
  - Begin after several days, and typically requires two to three weeks



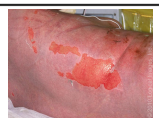
Cutaneous changes of Stevens-Johnson Syndrome
Generalized eruption of lesions that initially had a target-like appearance but then became confluent, brightly erythematous, and bullous. The patient had extensive mucous membrane involvement and tracheobronchitis.



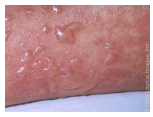
Cutaneous findings of Stevens Johnson Syndrome
Note the vesicles and bulla that are characteristic of the cutaneous findings in Stevens Johnson syndrome.



Mucosal changes in Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)
Changes similar to those observed in SJS/TEN can be observed also in erythema multiforme majus.

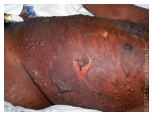


Toxic epidermal necrolysis
Diffuse erythema and large areas of denuded epidermis are present.

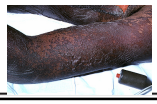


Toxic epidermal necrolysis
Multiple bullae overlying diffuse erythema are present.

Toxic epidermal necrolysis
Multiple bullae and large areas of denuded epidermis are present.



Toxic epidermal necrolysis
Usually caused by drugs, toxic epidermal necrolysis demonstrates widespread erythema and confluent vesiculation, leading to sloughing of the skin. Affected patients are at risk for hypernatremic dehydration and sepsis.



Bullous erythema multiforme
Detachment less than 10 percent of BSA *plus*
Typical targets *or*
Raised atypical targets
Stevens-Johnson syndrome
Detachment less than 10 percent of BSA *plus*
Widespread macules *or*
Flat atypical targets
Overlap Stevens-Johnson syndrome-Toxic epidermal necrolysis
Detachment between 10 and 30 percent of BSA *plus*
Widespread macules *or*
Flat atypical targets
Toxic epidermal necrolysis
With spots or without blisters
Detachment of greater than 30 percent of BSA *plus*
Widespread macules *or*
Flat atypical targets
Without spots
Detachment greater than 10 percent of BSA with large epidermal sheets *and*
Without any macules or targets

Literature review

Allopurinol(1)

HLA-B*58:01 is a risk factor for allopurinol induced DRESS and SJS/TEN in a Portuguese population.
[redacted] 2013 Apr 21.

- **OBJECTIVE**
  - ✓ Study the association of HLA-B*58:01 with allopurinol induced sCADR in a Portuguese population
- **METHODS**
  - ✓ Studied 25 patients (11M/14F, mean age 67.4y) with sCARD from allopurinol
  - ✓ Compared statistically with a control group of 23 allopurinol tolerant in dividuals and the control population
- **RESULTS**
  - ✓ HLA-B*58:01 was associated with a higher risk of Scadr
  - ✓ DRESS (OR=85.36, 95% CI: 32.52-224.04)
  - ✓ SJS/TEN (OR=99.59, 95% CI: 17.91-553.72)
- **CONCLUSIONS**

Allopurinol(2)

Allopurinol Hypersensitivity: A Systematic Review of All Published Cases, 1950-2012.
[redacted] 2013 Jul 20.

- **OBJECTIVE**
  - ✓ Review all published cases of allopurinol hypersensitivity (AH) documented in the literature in order to better understand the constellation of factors predisposing to this reaction
- **METHODS**
  - ✓ Literature search was conducted in MEDLINE and EMBASE to identify relevant articles published between January 1950 and December 2012
- **RESULTS**
  - ✓ Nine hundred and one patients (overall AH cohort) were identified from 320 publications
- **CONCLUSIONS**
  - ✓ Risk factors associated with AH, such as concomitant diuretic use, pre-existing renal impairment and recent initiation of allopurinol
  - ✓ A clear risk factor was the HLA-B*5801 status
  - ✓ High allopurinol dose, previously suggested to be a risk factor, was not confirmed as such

Allopurinol(3)

- **UpToDate**
  - Dermatologic: Rash
  - Gastrointestinal: Diarrhea, nausea
  - Hepatic: Alkaline phosphatase increased, liver enzymes increased
  - <1% (Limited to important or life-threatening): Stevens-Johnson syndrome, taste perversion, thrombocytopenia, toxic epidermal necrolysis
- **Micormedex**
  - Dermatologic: Rash (less than 1%), Stevens-Johnson syndrome (less than 1%), Toxic epidermal necrolysis (less than 1%)
  - Hematologic: Agranulocytosis, Aplastic anemia, Eosinophilia, Myelosuppression, Thrombocytopenia (0.6%)
  - Hepatic: Granulomatous hepatitis (less than 1%), Hepatic necrosis (less than 1%), Hepatotoxicity
  - Immunologic: Immune hypersensitivity reaction
  - Renal: Renal failure (less than 1%)

Nateglinide

- UpToDate
  - >10%: Upper respiratory infection (11%)
  - Central nervous system: Dizziness (4%)
  - Endocrine & metabolic: Hypoglycemia (2%), uric acid increased
  - Gastrointestinal: Diarrhea (3%), weight gain
  - Neuromuscular & skeletal: Back pain, (4%), arthropathy (3%)
  - Respiratory: Bronchitis (3%), cough (2%)
  - Miscellaneous: Flu-like syndrome (4%)
  - Case reports: Cholestatic hepatitis, hypersensitivity reactions (including pruritus, rash, urticaria), jaundice, liver enzymes increased
- Micormedex
  - Endocrine metabolic: Hypoglycemia (1.3% to 3%%)
  - Respiratory: Upper respiratory infection (10.5%)

Other suspected drugs

- UpToDate
  - Ceftazidime & Clopidogrel
    - ✓ <1% Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Sitagliptin
    - ✓ Stevens-Johnson syndrome, have been reported in postmarketing surveillance. Events have generally been noted within the first 3 months of therapy, and may occur with the initial dose
  - Furosemide & Spironolactone
    - ✓ Dermatologic: drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome, toxic epidermal necrolysis

Statistical

疑似因使用allopurinol導致不良反應之申請案例病徵統計

SOC 代碼	不良反應病徵	件數	百分比 (%)
10019805	肝膽不良反應		
	Acute hepatic failure	1	0.7
10021428	免疫系統不良反應		
	Drug hypersensitivity, Hypersensitivity syndrome	13	9
10040785	皮膚黏膜不良反應	131	90.3
	Stevens-Johnson syndrome	93	71
	Toxic epidermal necrolysis	21	16
	其他 [a]	17	13

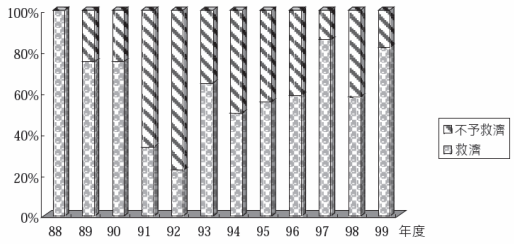
[a] 包括 skin rash, erythema multiforme, skin eruption, exfoliative dermatitis 等

個案基本資料分析及allopurinol使用情形

基本資料 (案件數 =145 件)	平均值 ± 標準差 (範圍)	案件數 (%)
性別		
男性		71(49%)
女性		74(51%)
平均年齡 (歲)	62.48±15.83 (19~92)	
平均使用劑量 (mg/day)	177.43±112.94 (50~900)	
處方地區		
北區		65(44.8%)
中區		34(23.4%)
南區		41(28.3%)
東區		5(3.4%)
處方來源之醫療院所類別		
醫院		125(86.2%)
診所		18(12.4%)
藥局 (自行購買)		1(0.7%)
使用目的 *		
痛風且有症狀描述		35(24.1%)
痛風性關節炎且有症狀描述		26(17.9%)
高尿酸血症		46(31.7%)
診斷為痛風或痛風性關節炎但無症狀描述且尿酸值偏高者		29(20.0%)
腎結石		4(2.8%)
慢性腎衰竭		1(0.7%)
無相關診斷		3(2.1%)

* 依病歷載明診斷名稱及是否有相關症狀描述記載。

歷年疑似因使用allopurinol 致藥害之審議結果

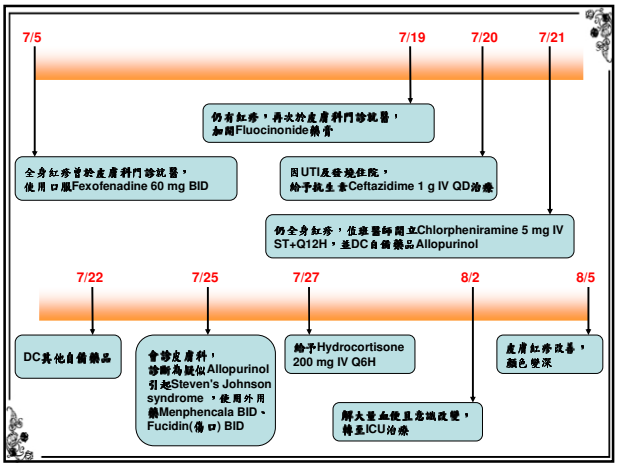


疑似因使用allopurinol導致不良反應之申請案例給付情形

給付情形	案件數	救濟金額（千元）	分項百分比 (%)	總計百分比 (%)
總案件數	145			-
給予救濟	90	3,588	-	62.1
嚴重疾病+	45	193	50	
障礙#	2	215	2.2	
死亡	43	3,180	47.8	
不予救濟及其原因*	55	-	-	37.9
有事實足以認定藥害之產生應由藥害受害人、藥物製造業者或輸入業者、醫師或其他人負及責任	18	-	32.7	
未依藥物許可證所載之適應症或效能而為藥物之使用	29	-	52.7	
藥物不良反應未達死亡、障礙或嚴重疾病之程度	2	-	3.6	
常見且可預期之藥物不良反應	1	-	1.8	
與使用藥品無關	3	-	5.5	
其他	2	-	3.6	

+ 適用藥害救濟法之嚴重疾病，限因藥物不良反應致危及生命、導致病人住院、延長病人住院時間、需作處置以防止永久性傷害者。
# 障礙：指符合身心障礙者保護法令所定障礙類別等級者。但不包括因心理因素所導致之情形。
* 參考現行藥害救濟法第 13 條之規定處理。

Summary



結論

- **Allopurinol**
  - **Gout (chronic): Oral**
    - ✓ Mild: 200-300 mg/day
    - ✓ Severe: 400-600 mg/day
    - ✓ Initiate dose at 100 mg/day and increase weekly to recommended dosage
    - ✓ Maximum daily dose: 800 mg/day
  - **予以通報Allopurinol為此次不良反應的可疑藥物，並為病患申請藥害救濟**
  - **HLA-B*58:01基因檢測的必要性**
- **Nateglinide**
  - **Management of type 2 diabetes mellitus: Oral**
    - ✓ Initial and maintenance dose: 120 mg 3 times/day, 1-30 minutes before meals
    - ✓ May be given alone or in combination with metformin or a thiazolidinedione
    - ✓ Patients close to HbA1c goal may be started at 60 mg 3 times/day
  - **Nateglinide不予通報**

Thanks for your attention!