Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

Name of candidate (print and sign):
Hospital and Unit: Specialty:
Name of supervisor (print and sign):
Date(s) and place (hospital) of patient encounter: 31/07/2020
Date of report submission: 10/03/2021

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: A typical case of carbamazepine related Stevens-Johnson syndrome and toxic epidermal necrolysis amongst patients of Chinese ethnic origin

Case history:

A 29-year-old Chinese lady, Ms. X, has a background history of anxiety and depression since 2012 and was under follow up in the private sector. She is allergic to penicillin. Her regular medications include paroxetine, pregabalin, diazepam and flunitrazepam. She was diagnosed with bipolar affective disorder (BAD) on 15/07/2020. She presented with grandiose ideations, overspending and impulsive causal sexual intercourses with multiple partners. She was then started on aripiprazole, quetiapine and lorazepam. Paroxetine and diazepam were tapered off. Carbamazepine was started on 20/07/2020 for her mood symptoms by private psychiatrist.

On 28/07/2020 she developed generalised non-pruritic erythematous rash all over her trunk, back and limbs together with mild shortness of breath, sore throat, odynophagia and dysphagia. There were no urogenital symptoms. She was admitted to a private hospital the next day. Her skin lesion was described as maculopapular with no evidence of Nikolsky's sign

or any mucosal involvement but she was noted to have fever. Throat examination revealed exudates and erythema over bilateral tonsils. She was suspected to have Stevens-Johnson syndrome or toxic epidermal necrolysis (SJS/TEN) given the history of recent carbamazepine consumption. Carbamazepine was stopped immediately, and doxycycline and ciprofloxacin were started whilst await results of her septic workup. Her anti-streptolysin O titre (ASOT) was mildly elevated, 337 IU/ml (normal range <200 IU/ml). A skin biopsy on her back was performed which showed interface dermatitis with a few necrotic keratinocytes indicating possible infective exanthem verse exanthematous drug eruption. One day after admission, there were increasing extent of her rash and her eyes started to feel gritty. She developed high fever up to 40 degree Celsius and hypotension. Clindamycin, azithromycin, hydrocortisone and intravenous immune globulin (IVIG) were administered. Intensive care support was suggested in the private hospital but she preferred continual care in the public hospital due to financial reason.

On arrival at our A&E, Ms. X was haemodynamically unstable requiring high dose inotropic support. She was admitted to the Intensive Care Unit (ICU) directly. On physical examination, there was extensive diffuse erythema with multiple bullae and desquamation covering her face, trunk, back and all four limbs equivalent to 80% of body surface area. There was crusting of the lips, buccal mucosa and genitalia (Figure 1). Conjunctivitis of both eyes were noted. These findings progressed rapidly within hours of admission. Given her clinical manifestation and recent initiation of carbamazepine, human leukocyte antigen (HLA)-B*1502 was immediately checked and the result came back to be detected. The diagnosis of carbamazepine-induced TEN was concluded. The culprit drug was discontinued when she was first presented. An alert was input into her personal medical record. She was placed in a single room with reverse-isolation. She was managed with aggressive intravenous fluids, broad-spectrum antibiotics including levofloxacin, vancomycin and clindamycin, inotropic support and further IVIG infusion.

Her pain was adequately controlled with paracetamol, tramadol and morphine. A nasogastric tube was inserted for feeding and optimisation of nutrition. Unfortunately, feeding was not well tolerated, and she developed diarrhoea which further contributed to *Escherichia coli* bacteriaemia. Amikacin and metronidazole were administered. Total parenteral nutrition

was started to optimise her nutrition. Diarrhoea subsequently subsided. She was in an immunocompromised state with persistent fever. Sputum culture was positive for multidrug-resistant *Acinetobacter* which responded to tigecycline. Urine culture from urinary catheter was positive for *candida albicans* which responded well with fluconazole. The *clostridium difficile* stool culture was negative. A repeated ASOT was insignificant. *Mycoplasma pneumoniae* antibody and the human immunodeficiency viruses were unremarkable. Her fever subsequently subsided and was able to wean off further inotropic support.

The burns unit was consulted but no bed was available. Plastic surgeon was consulted and advice for wound management was followed. Ophthalmologist was consulted to evaluate for any ocular involvement. Bilateral corneal abrasions, epithelial defects and minimal pseudomembrane formation were detected which was affecting her vision. Prednisolone acetate, levofloxacin and lubricating eye drops were given.

The overall condition of Ms. X started to improve (Figure 2). Swallowing was reviewed by the speech therapist and oral feeding resumed safely. Nasogastric tube and central venous catheters were removed. She was discharged to the general ward after two weeks of ICU stay.

Ms. X continued to recover. She underwent rehabilitation and her mobility returned to her pre-morbid state. Her skin healed nicely without any major scarring. Her vision improved. She was not in any pain and her mood was stable. Psychiatrist reviewed her mental status and deemed her anxiety, depression and BAD were in remission and advised her to take lorazepam as needed only. She opted to continue follow up by her private psychiatrist. Details of carbamazepine related TEN was relayed back and she was educated on avoidance of the offending drug and also drug of similar groups such as oxcarbazepine, phenytoin and lamotrigine in the future as further exposure may be fatal. After one month of hospitalisation for TEN, Ms. X have made excellent recovery and was discharged home. She continued to make good progress and there were no cosmetic issues with her skin and her vision returned back to normal.

Discussion and literature review

This is a case of carbamazepine-induced toxic epidermal necrolysis (TEN). SJS and TEN describe a spectrum of severe mucocutaneous reactions manifested as extensive blistering and epithelial sloughing. SJS is the less extensive form (epidermal detachment <10% body surface area) and TEN is the more extensive form (detachment >30% body surface area). [1] It is largely a clinical diagnosis. A skin biopsy is useful to exclude other conditions such as staphylococcal scaled skin syndrome and bullous pemphigoid.

The incidence of SJS/TEN in Southeast Asia is largely undetermined due to the lack of epidemiological studies and the disease rarity. A nationwide population-based study over four years in Korea estimated an incidence rate of 5.9 cases per million per year. [2] The estimated incidence of SJS/TEN in a UK-based observational study over eighteen years was 5.76 cases per million per year and found that Asian patients had a two-fold increased risk of SJS/TEN compared to Caucasian patients. [3] This is likely due to the strong association of human leukocyte antigen (HLA)-B*1502 within the Asian population causing high susceptibility to SJS/TEN.

Although SJS/TEN is a rare condition, it can be potentially lethal due to its extensive systemic involvement and risks of multi-organ failure. The survivors often develop significant long-term sequelae. The overall mortality is 30%. Patients with sepsis, acute respiratory distress syndrome, acute renal failure, older age and presence of co-morbidities are at higher risk of death. Fortunately, this is not applicable in Ms. X's case. Studies have shown that management of SJS/TEN patients in a burns centre improves survival. [1], [4]

Drugs are the main trigger for SJS/TEN. The next common trigger is *Mycoplasma pneumoniae* infection which usually occurs in children. The pathophysiology of drug-induced SJS/TEN involves widespread epithelial keratinocyte apoptosis and necrosis through a cell-mediated cytotoxic reaction. Drugs directly bind to the major histocompatibility complex (MHC) class I and T cell receptor which caused drug-specific cytotoxic T cells to kill keratinocytes directly. Current evidence found that the release of soluble death mediators such as granulysin is the key for keratinocyte apoptosis. [5]

Drugs that are high risk of causing SJS/TEN include allopurinol, carbamazepine, phenytoin, sulfonamides and oxicam non-steroidal anti-inflammatories such as piroxicam. Amoxicillin, oxcarbazepine and diclofenac are found to have a less significant association. Apart from conventional drugs, herbal remedies and new biologicals have been considered as causative agents. [6] A validated algorithm termed ALDEN (ALorithm of Drug causality in Epidermal Necrolysis) is available to help define drug causality in SJS/TEN retrospectively after acute phase of illness. There is a latent period of 5-28 days between onset of SJS/TEN and initiation of the culprit drugs. [1] It was 8 days in Ms. X's case.

Carbamazepine is widely used as an anticonvulsant, analgesia for trigeminal neuralgia and a mood-stabilising drug in BAD as in Ms. X's case. It is strongly associated with HLA-B*1502. Not only is a thorough medication history important when come across a case of SJS/TEN, attention should also be paid on the ethnicity. There is a well-known association between HLA-B*1502 and Han Chinese. A study conducted in Taiwan concluded a 100% association between HLA-B*1502 allele and carbamazepine-induced SJS/TEN in Han Chinese with a significantly high odds ratio of 2504 compared with carbamazepine-tolerant subjects. [7] A local case-control study conducted at a tertiary hospital in Hong Kong also supported the Taiwanese study and showed 100% association ($p=1.48x10^{-4}$). It also found that patients with lamotrigine and phenytoin-induced SJS/TEN also had the HLA-B*1502 allele perhaps due to a similar immune response. However, larger studies are needed to confirm this postulation. Furthermore, this study was limited by its small sample size which resulted in a wide confidence interval. [8]

Management of SJS/TEN requires a multidisciplinary approach, preferably co-ordinated by dermatologist or plastic surgeons in a burns centre or an ICU with experienced wound care team. Immediate withdrawal of potential culprit drug, carbamazepine in this case is mandatory. Patient should be barrier-nursed in a single room controlled for humidity and pressure-relieving mattress. Surgical debridement of infected skin may be needed in cases of uncontrolled sepsis. Supportive management includes adequate fluid resuscitation to prevent end-organ hypoperfusion and shock from large insensible fluid loses. Adequate nutrition (20-25 kcal/kg/day in early catabolic phase) to facilitate wound healing. Sufficient analgesia to ensure comfort at rest. Prompt treatment for infections and prevention of venous

thromboembolism and stressed-related peptic ulcers.

Close monitoring and prompt treatment of mucosal involvement in particular ophthalmic sequelae in our case is of vital importance to prevent long-term visual impairment. Long term oral, dental, vulvovaginal, pulmonary and psychological complications should be taken into consideration and prompt referral for specialist assessments if suspected.

There is currently not enough strong evidence for adjunctive therapy for SJS/TEN due to rarity of the disease. There is limited and conflicting evidence for the use of IVIG in SJS/TEN but it's use has been favourable in our locality. IVIG carries risks of renal failure, haemolysis and thrombotic complications especially in older patients or those with pre-existing renal or cardiovascular disorders. The use of systemic corticosteroids is controversial. Theoretically, it increases the risks of sepsis and protein catabolism which decreases rate of epithelialisation. Hence, its use in patient with extensive skin involvement is not recommended. Cyclosporin A has a theoretical benefit in SJS/TEN demonstrated in case series due to its ability to inhibit T cell activation. Tumour necrosis factor inhibitor such as infliximab has shown beneficial effects in a small number of patients. In refractory cases, plasmapheresis has been reported to be beneficial in several case reports and small series. [1]

In 2007, the United States Food and Drug Administration recommended to screen all patients of Asian ancestry for HLA-B*1502 allele prior starting treatment with carbamazepine. The Drug Office of the Department of Health in Hong Kong has issued a safety alert in 2016 that HLA-B*1502 allele test results should be obtained prior prescribing carbamazepine and suggests for alternative therapy if test is positive. A study conducted in southern mainland China showed that the HLA-B*1502 allele test has a 100% sensitivity, 86.25% specificity, 45% positive predictive value and 100% negative predictive value. [9] Genotyping for HLA-B*1502 allele was proven to be cost-effective for Chinese in Singapore. [10]

In conclusion, Ms. X has demonstrated the importance of screening HLA-B*1502 allele especially in patients of Han Chinese origin prior the use of carbamazepine to prevent the potential devastating consequences of developing SJS/TEN.

Tables and figures (where applicable) (no more than two figures)

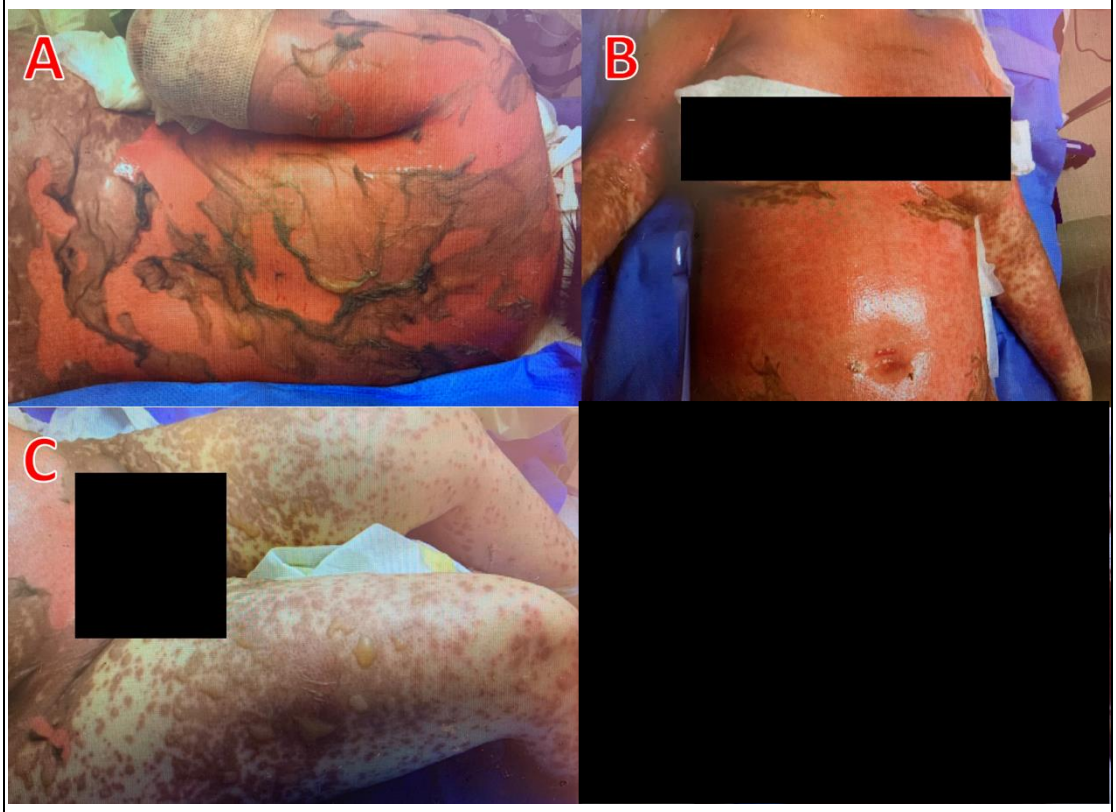

Figure 1. Clinical photo showing diffuse erythema with multiple bullae and desquamation over back (A), trunk (B) and legs (C). Crusting of lips and erythematous maculopapular rash over face (D) – *Note: photo D showing head of patient is redacted for upload of this report to College web site*.

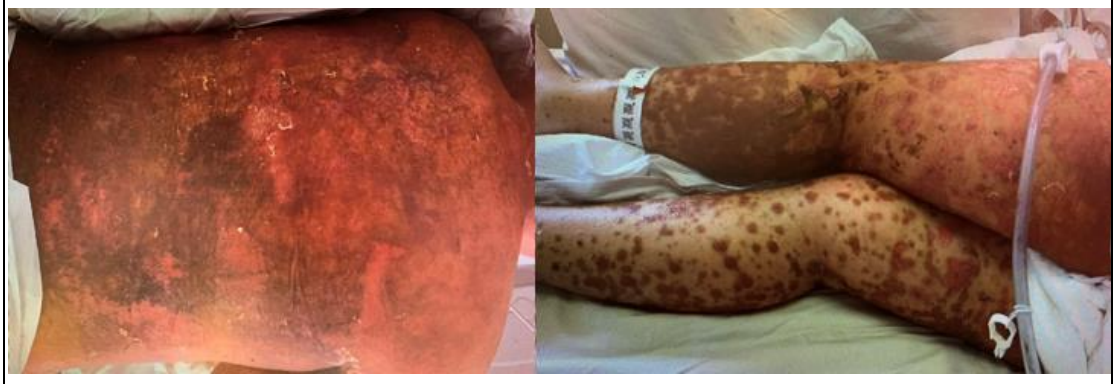

Figure 2. Clinical photo of skin showing signs of healing, one month after symptoms onset

Reference (not more than 10)

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No of words in Case History and Discussion (excluding references): 1893

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)

* Supervisors must go over the Case Report with the Trainees, advise Trainees whether further amendments are necessary, review the Originality/Similarity Report prepared by Trainees, adherence to the required format, sign on the report and remind Trainees on issues related to copyright and plagiarism.