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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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WHO-UMC-HSA Inter-Regional Pharmacovigilance Training Workshop 2021

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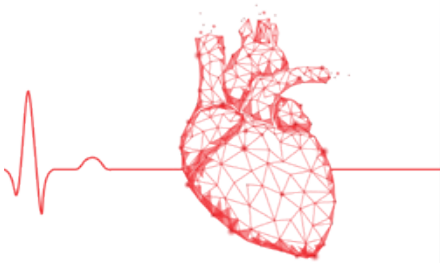
The WHO-UMC-HSA Inter-Regional Pharmacovigilance (PV) Training Workshop which was conducted virtually in Singapore for the first time in September 2021, was attended by 72 international participants from the ASEAN countries, Belgium, France, Nepal and Saudi Arabia. The participants included both regulators and members of the industry. The event marked the fifth training collaboration between the World Health Organization (WHO), the Uppsala Monitoring Centre (UMC) and HSA. This year, it was co-organised with Duke NUS Centre of Regulatory Excellence (CORE).

AE Case in Focus 1: Test Yourself

What could have caused the chest discomfort in this patient?

Pg 6 - 7

This is a case of a male patient in his early 20s who presented with chest discomfort several days after vaccination with Dose 1 of his mRNA COVID-19 vaccine. The chest discomfort was non-pleuritic but changed in severity with position; worsened with lying down and improved with sitting up. It was also associated with palpitations, but there were no symptoms of dizziness or loss of consciousness. There was no significant past medical history. There were no symptoms to suggest recent infection and no preceding strenuous exercise. His electrocardiogram test demonstrated sinus rhythm with high take-off of ST segments in the anterior chest wall leads. His troponin test was negative. The patient's symptoms resolved spontaneously after several days without medication.



AE Case in Focus 2: Test Yourself

What could have caused the patient's cough with haemoptysis?

Pg 7 - 8

This is a case of a young adult female who presented to the Emergency Department with coughing and two episodes of haemoptysis. The blood stain from haemoptysis was the size of a 5-cent coin, with small blood clots that stained her mask. She had reported haemoptysis the day before and two weeks prior. During history taking, she revealed that she had been using flavoured electronic cigarettes (e-cigarettes) regularly over the past 5 years. She was also a cigarette smoker of three pack-years. Her medical history includes a history of recurrent trivial haemoptysis since 2017. The investigation previously done included acid-fast bacilli culture tests in 2017 and 2019, of which the results were negative. Her otolaryngology review in 2017 and 2019 did not reveal any upper airway cause and an esophageal gastroduodenoscopy performed in 2018 was normal. A computed tomography (CT) scan of the thorax in 2020 showed minor linear atelectasis. No focal consolidation or suspicious lung lesions were detected. Her clinical examination was unremarkable and her admitting chest X-ray showed mild lower zones infiltrates.

HSA is going paperless: Removal of fax option for adverse event reporting

In line with the nation's efforts to go paperless and taking into consideration that adverse event (AE) reports received by HSA are largely submitted electronically, HSA's AE reporting channels will be going fully digital starting 1 April 2022. We will cease the option of using fax as a channel of reporting. Healthcare professionals are encouraged to report AEs online via hsa.gov.sg/adverse-events or email them to HSA_productsafety@hsa.gov.sg

Dear Healthcare Professional Letters on safety concerns

How to report suspected AEs to HSA?

For any suspected AEs, please report to us via the following:

- HSA_productsafety@hsa.gov.sg
- https://www.hsa.gov.sg/adverse-events

For any enquiries or assistance on AE reporting, please call us at 6866 1111

All website references were last accessed on 1 December 2021.

ALLOPURINOL-INDUCED SEVERE CUTANEOUS ADVERSE REACTIONS AND THE ROLE OF HLA-B*5801 GENOTYPING – A REMINDER

Key Points

- From March 2016 to October 2021, HSA received 80 cases of allopurinol-induced SCAR. Notably, most of the cases had risk factors for SCAR, such as older age and/or renal impairment. Similar risk factors were observed among the 14 cases with HLA-B*5801 status reported, out of which the majority were tested after they had developed SCAR and were HLA-B*5801 positive
- While HLA-B*5801 genotyping is not routinely recommended for new patients initiating allopurinol, healthcare professionals may consider genotyping patients who have pre-existing risk factors for allopurinol-induced SCAR such as renal impairment and older age, to identify those who are at a greater risk of allopurinol-induced SCAR
- Healthcare professionals are advised to consider and discuss with their patients the benefits of treatment and risks, including SCAR, as well as the availability of the HLA-B*5801 genotyping test before prescribing allopurinol. Healthcare professionals are also advised to educate patients on the recognition of early signs and symptoms of SCAR and the importance of prompt drug withdrawal and medical consultation at the first sign of rash

HSA would like to remind healthcare professionals about the risk of severe cutaneous adverse reactions (SCAR) with the use of allopurinol and the role of HLA-B*5801 genotyping prior to therapy initiation. In March 2016, the Ministry of Health (MOH) and HSA jointly issued a Dear Healthcare Professional Letter to inform that HLA-B*5801 genotyping prior to the initiation of allopurinol therapy is not required as standard of care.[1] Nonetheless, healthcare professionals were also advised that they may consider genotyping patients who have pre-existing risk factors for allopurinol-induced SCAR such as renal impairment and older age, to identify those who are at a greater risk of allopurinol-induced SCAR.

Allopurinol is a uricosuric agent indicated for reducing urate/uric acid formation in gout and other conditions such as nephrolithiasis. It has been registered in Singapore since 1989 and there are currently seven registered allopurinol-containing products locally.

Local cases of allopurinol-induced SCAR

From March 2016 to 1 October 2021, HSA received 80 cases of allopurinol-induced SCAR, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Six of these cases were fatal. Allopurinol was the sole suspected agent in majority (n=69, 86%) of the cases. Notably, most of the cases had risk factors for SCAR, such as older age and renal impairment. Of the 71 cases with age reported, close to two-thirds (65%) were aged 60 years and above. Renal function was reported in 42 cases, of which approximately two-thirds (64%) had renal impairment. Of the 41 cases where allopurinol dose was reported, nearly two-thirds (63%) received allopurinol 100mg or below daily while the remaining cases received daily doses ranging from more than 100mg to 300mg.

Information on when the HLA-B*5801 genotyping test was conducted, and the corresponding test results were available for 12 cases and 14 cases respectively. The majority of the cases were tested following the development of SCAR (71%) and were HLA-B*5801 positive (86%). Most of the HLA-B*5801-positive cases were aged 60 years and above (92%) and/or reported renal impairment of varying degrees (~67%). The remaining two HLA-B*5801-negative cases were aged 60 years and above and had chronic kidney disease.

About HLA-B*5801 genotyping test

The HLA-B*5801 genotyping test has high sensitivity and selectivity of over 80% for allopurinol-induced SCAR.[2] However, the rarity of allopurinol-induced SCAR (i.e. around 3 out of 1,000 patients on allopurinol may develop SCAR) leads to a low positive predictive value (PPV) of the HLA-B*5801 test (estimated PPV: 2%, i.e. approximately 2 out of 100 HLA-B*5801-positive people starting allopurinol may develop SCAR). The low PPV, together with a lack of alternative cost-effective urate-lowering therapy options, limit the overall value of routine genotyping from a health-systems perspective. Testing for the allele may be more useful in treatment decision-making if the patient is assessed to already be at a higher risk of allopurinol-induced SCAR with renal impairment or older age.[3]

Currently, the HLA-B*5801 genotyping test is available at the DNA Diagnostic & Research Laboratory at KK Women's and Children's Hospital, the Tan Tock Seng Hospital Molecular Diagnostic Laboratory, and the Tissue Typing Laboratory at HSA. The estimated turnaround time for the test result is one to seven working days.

HSA's advisory

Healthcare professionals are reminded of the following advisory, when considering the use of allopurinol in new patients:

- Allopurinol should be used with caution especially in older patients with renal impairment. Consider starting at a low dose and titrate accordingly.
- While HLA-B*5801 genotyping is not routinely recommended for new patients initiating allopurinol, healthcare professionals may consider genotyping patients who have pre-existing risk factors for allopurinol-induced SCAR such as renal impairment and older age, to identify those who are at a greater risk of allopurinol-induced SCAR. While patients who have tested negative for the HLA-B*5801 allele are at lower risk of developing allopurinol-induced SCAR, they can still develop SCAR as there are non-genetic factors that increase the risk. Hence, genetic testing, when ordered for at-risk patients, should not substitute for appropriate clinical vigilance and patient management.
- Healthcare professionals are advised to consider and discuss with their patients the benefits of treatment with allopurinol and its risks, including SCAR, as well as the availability of pre-treatment HLA-B*5801 genotyping test before prescribing allopurinol.
- Healthcare professionals are also advised to educate patients on the recognition of early signs and symptoms of SCAR and the importance of prompt drug withdrawal and medical consultation at the first sign of rash. Patient educational materials such as the Patient Education Aid in the Appropriate Care Guide[3] and Consumer guide on Safe Use of Allopurinol[4] may be used and distributed to patients during medication counselling.

Healthcare professionals are encouraged to report any suspected serious adverse reactions related to allopurinol to the Vigilance and Compliance Branch of HSA.

References

1. *https://www.hsa.gov.sg/announcements/safety-alert/allopurinol-induced-serious-cutaneous-adverse-reactions-and-the-role-of-genotyping*
2. *Front Pharmacol 2020; 11: 567048*
3. *ACE Appropriate Care Guide 'Gout Achieving the Management Goal' dated 20 December 2019*
4. *https://www.hsa.gov.sg/consumer-safety/articles/safe-use-of-allupurinol*

Useful Information

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA ADR News Bulletin. Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

UPDATES ON ADULTERATED PRODUCTS REPORTED TO HSA

Key Points

- Weight loss products were the most common category of adulterated products detected by HSA in the period of 2019 to October 2021 followed by sexual enhancement products
- The most common adulterant detected in weight loss products was sibutramine, a banned substance since 2010 due to an increased risk of heart attack and strokes
- Healthcare professionals play an important role in helping HSA detect potentially adulterated products. A careful history-taking, including non-medicinal or complementary health products used by patients for purposes such as weight loss or sexual enhancement, would help in the detection of potentially adulterated products

From 2019 to October 2021, HSA detected 54 adulterated products and issued 20 press releases to warn the public on the dangers of these products and not to purchase them. HSA was alerted to these products through adverse event (AE) reports by healthcare professionals and HSA's surveillance activities, feedback from consumers, members of the public and the Immigration & Checkpoints Authority (ICA) who had intercepted the parcels upon importation. HSA's Pharmaceutical Laboratory had tested the products and found potent medicinal ingredients and banned substances (sibutramine) present in these products. Majority of the adulterated products were marketed for slimming/weight loss (57%) and for sexual enhancement in men (15%). The most common adulterant found in the slimming and weight loss products was sibutramine, a prescription-only weight loss medicine in Singapore which has been banned since 2010 due to an increased risk of heart attack and strokes. Other adulterants detected in the other products were erectile dysfunction medicines (e.g. tadalafil, sildenafil), steroids (e.g. dexamethasone, betamethasone, clobetasol, prednisolone), nonsteroidal anti-inflammatory drugs (e.g. diclofenac, meloxicam), antihistamines (e.g. chlorpheniramine, diphenhydramine), antibiotics (e.g. amoxycillin, ciprofloxacin, sulfamethoxazole, trimethoprim), antifungals (e.g. ketoconazole, griseofulvin), diuretics (e.g. frusemide) and laxatives (e.g. sennosides).

In 2021, HSA issued four press releases to alert the public on the following 12 adulterated products, of which ten were sold for weight loss and two were marketed for sexual enhancement in men.

'Bobba Fitz' and 'Bobba Tox'

HSA was alerted to 'Bobba Fitz' and 'Bobba Tox' by a female consumer who experienced heart palpitations, constipation and mood swings after taking 'Bobba Fitz' and 'Bobba Toxx' for weight loss. 'Bobba Fitz' was labelled to contain natural ingredients such as whey protein, cocoa powder and Garcinia Cambogia (a fruit-derived ingredient), but HSA tested it and found the banned substance, sibutramine. 'Bobba Fitz' was often sold in a set with another product, 'Bobba Toxx', which was also tested to contain a laxative (sennosides), where the amount detected was about four times the usual therapeutic dose. Both products were packaged in boxes of ten powder sachets. The products were sold on local e-commerce and social media platforms. HSA had worked with various platform administrators including Shopee, Lazada, Facebook and Instagram to promptly remove the affected listings and issued warnings to the respective sellers. HSA issued a press release on 1 March 2021 which can be found on HSA's website: https://www.hsa.gov.sg/announcements/press-release/bobba-fitz

Figure 1. 'Bobba Fitz'

Figure 2. 'Bobba Toxx'

'Flash Slim', 'Leedee Botanical Beverage Mix Pineapple Juice Powder with African Mango', 'Quinn S Amyera' and 'Schocolite Double Chocolate Cookies Drink with Hoodia Gordinii Extract and L-Carnitine'

A male consumer was taken in by an advertisement of 'Flash Slim' posted on an e-commerce website, which claimed that the product was "15X more effective to burn stubborn fat" with "results guaranteed within 1-5 days". Although he had lost some weight after taking the product, he also experienced serious adverse effects such as palpitations, nausea, insomnia and excessive sweating.

HSA also received feedback from members of the public who suspected that 'Leedee Botanical Beverage Mix Pineapple Juice Powder with African Mango', 'Quinn S Amyera' and 'Schocolite Double Chocolate Cookies Drink with Hoodia Gordinii Extract and L-Carnitine' may contain potent ingredients because of the exaggerated claims made. These products were marketed for slimming and claimed to "burn fats quickly", "show results [in] as early as 7 to 14 days" and "increase metabolism".

The four products were tested and found to be adulterated with sibutramine, a banned substance. HSA had since worked with the various e-commerce platform and social media administrators to remove the affected listings and issued warnings to the respective sellers. A press release was issued on 25 March 2021 and published on HSA's website: https://www.hsa.gov.sg/announcements/press-release/four-products-sibutramine-25mar

Figure 3. 'Flash Slim'

Figure 4. 'Leedee Botanical Beverage Mix Pineapple Juice Powder with African Mango'

Figure 5. 'Quinn S Amyera'

Figure 6. 'Schocolite Double Chocolate Cookies Drink with Hoodia Gordinii Extract and L-Carnitine'

'Miracle Gold Candy', 'C4 Candy' and 'Coco Hotz Cocoa Drink'

Officers from the Immigration & Checkpoints Authority (ICA) had alerted HSA to 'Miracle Gold Candy' when they detected anomalies during the importation of the product. Another candy product, 'C4 Candy', was reported to HSA by a member of the public who suspected that the product could be adulterated. Both products were packaged as candies and marketed for sexual enhancement in men. The products' labels carried exaggerated claims which were not expected for candy products, such as "increase the strength and health of men" for 'Miracle Gold Candy', and "prevent premature ejaculation" and "help those with gout, diabetes and high blood pressure" for 'C4 Candy'. Both products were tested by HSA to contain tadalafil, a prescription medicine used to treat erectile dysfunction. Of note, 'Miracle Gold Candy' was found to contain up to over 30 times the usual daily dose of tadalafil, which increases the risk of stroke and heart attack significantly.

HSA had received feedback from a consumer who suspected that 'Coco Hotz Cocoa Drink' could be an adulterated product due to its exaggerated claims. 'Coco Hotz Cocoa Drink' was touted for slimming with claims such as "burn fat quickly" and "control appetite". The product was tested and found to contain dexamethasone, a potent steroid. Long-term unsupervised use of steroids can cause serious adverse effects including increased blood glucose levels (which may lead to diabetes) and Cushing's syndrome. HSA had since worked with various e-commerce platform and social media administrators to remove the affected listings and issued warnings to the respective sellers. The press release was issued on 8 October 2021 and published on HSA's website: https://www.hsa.gov.sg/announcements/press-release/miraclegold-c4candy-cocohotz

Figure 7. 'Miracle Gold Candy'

Figure 8. 'C4 Candy'

Figure 9. 'Coco Hotz Cocoa Drink'

'Magic Mocha', 'Thao Moc Ho Tro Giam Beo Cenly' and 'Cynthia Beauty EazyS Instant Coffee Powder'

'Magic Mocha', 'Thao Moc Ho Tro Giam Beo Cenly' and 'Cynthia Beauty EazyS Instant Coffee Powder' were reported to HSA by three separate consumers who had bought the products from local e-commerce and social media platforms. They reported experiencing adverse effects such as palpitations, nausea, extreme thirst, migraine and/or dizziness after taking these products. The products were marketed for slimming with misleading claims such as "fast-acting", "fat-burning", "reduce fat storage" and "accelerate the breakdown of stubborn fat". HSA's analysis of these products showed that they contained the banned substance, sibutramine. HSA had quickly issued warnings to the sellers and the platform administrators have since removed the affected listings. The press release was issued on 10 November 2021 and published on HSA's website: https://www.hsa.gov.sg/announcements/press-release/threeconsumers_adverseeffects

Figure 10. 'Magic Mocha'

Figure 11. 'Thao Moc Ho Tro Giam Beo Cenly'

Figure 12. 'Cynthia Beauty EazyS Instant Coffee Powder'

Conclusion

Products adulterated with potent medicinal ingredients, including banned substances such as sibutramine, are harmful and can cause serious adverse effects in consumers. Healthcare professionals play an important role in helping HSA detect potentially adulterated products. A careful history-taking, including non-medicinal or complementary health products and other supplements used by patients for purposes such as weight loss or sexual enhancement, would help in the detection of potentially adulterated products. Healthcare professionals are advised to report suspected adverse events associated with the use of adulterated products to the Vigilance and Compliance Branch of HSA.

Healthcare professionals are encouraged to visit the HSA website at https://go.gov.sg/hsa-press-releases

WHO-UMC-HSA INTER-REGIONAL PHARMACOVIGILANCE TRAINING WORKSHOP 2021

The WHO-UMC-HSA Inter-Regional Pharmacovigilance (PV) Training Workshop which was conducted virtually in Singapore for the first time in September 2021, was attended by 72 international participants from the ASEAN countries, Belgium, France, Nepal and Saudi Arabia. The participants included both regulators and members of the industry. The event marked the fifth training collaboration between the World Health Organisation (WHO), the Uppsala Monitoring Centre (UMC) and HSA, with the previous workshops being conducted in 2010, 2012, 2015 and 2018.

Co-organised with Duke NUS Centre of Regulatory Excellence (CORE), the aim of the workshop was to equip participants with the necessary skills to further strengthen PV capabilities within their regions, especially during the COVID-19 pandemic. These objectives are aligned with WHO and UMC's continual drive to communicate the importance of drug safety and PV among countries. For the first time, the training was attended by participants from the European region including France and Belgium.

The theme of this year's training event was 'Enhancing Preparedness for Pharmacovigilance' and the event provided the opportunity and platform to allow participants from the regulatory authorities and industry to work together to strengthen drug safety. Key topics covered in the training included the following: (i) Vaccine safety and vaccine-related events (including COVID-19 vaccines); (ii) Global Benchmarking Tool (GBT) for PV; (iii) Risk management plans and PV communications; (iv) Digital innovations in enhancing PV. These topics were conducted by a team of local and international experts in the field of drug safety and vaccines, including Dr Shanthi Pal, Mr Takahiro Goto, Ms Isabelle Sahinovic, Mr Hiiti Sillo and Mr Brian Yau from the WHO, Dr Helena Sköld, Dr Elki Sollenbring, Dr Sara Vidlin and Dr Mónica Tarapués from the UMC, Mr Rajesh Ghosh from Roche, Dr Jean-Christophe Delumeau from Bayer and Ms Christine Ho from HSA. The sessions were followed by hands-on exercises to further enhance their understanding on these topics. Ms Nidhi Swarup, Founder and President of Crohn's & Colitis Society of Singapore (CCSS) was also invited to share insights on patients' role in PV communications. Following the end of workshop, a separate Regulator's session on Emergency Use Listing (EUL) and Risk Management Plan (RMP) for COVID-19 vaccines was conducted by Dr Carmen Rodriguez-Hernandez.

Overall, the participants provided good feedback on the training workshop, rating the workshop as either good or excellent and a large number of participants expressing that the quality of course content, pace of the lectures, duration of lectures and relevancy and usefulness of lecture materials provided were excellent.

Figure 1. CEO of HSA, Dr. Mimi Choong providing Opening Remarks at the WHO-UMC-HSA Pharmacovigilance Training Workshop 2021

Figure 2. Participants of the WHO-UMC-HSA Inter-Regional Pharmacovigilance Training Workshop 2021

AE CASE IN FOCUS 1: TEST YOURSELF

A male patient in his early 20s presented with chest discomfort several days after vaccination with Dose 1 of his mRNA COVID-19 vaccine. The chest discomfort was non-pleuritic but changed in severity with position; worsened with lying down and improved with sitting up. It was also associated with palpitations, but there were no symptoms of dizziness or loss of consciousness. There was no significant past medical history. There were no symptoms to suggest recent infection and no reported preceding strenuous exercise. On examination, there was no evidence of fluid overload, fever or haemodynamic instability. His lung auscultation was clear. No pericardial rub was detected. His electrocardiogram test demonstrated sinus rhythm with high take-off of ST segments in the anterior chest wall leads. His troponin test was negative. A decision was taken after discussion with the patient and his family not to undertake cardiac MRI (CMR) due to the significant cost of the investigation. The patient's symptoms resolved spontaneously after several days without medication.

Question: What could have caused the chest discomfort in this patient?

HSA would like to thank Dr. Chong Jun Hua, Consultant Cardiologist at the National Heart Centre for contributing this article.

ANSWER TO AE CASE IN FOCUS 1: TEST YOURSELF

The patient was diagnosed with mRNA COVID-19 vaccine-induced pericarditis based on his medical history, examination, and investigation results. An increased risk of pericarditis and myocarditis have been associated with the use of mRNA COVID-19 vaccines, particularly in younger males. No treatment was given, and he had recovered spontaneously on follow-up. He was subsequently referred for consideration of non-mRNA COVID-19 vaccine alternatives.

Myocarditis associated with COVID-19 infection and mRNA COVID-19 vaccines

COVID-19 infection can cause cardiovascular sequelae such as myocardial inflammation and inflammation of the blood vessels, and patients with pre-existing cardiovascular disease, hypertension and associated conditions are more likely to experience worse outcomes.[1] In contrast, cases of mRNA vaccine-associated myocarditis have mostly (96%) been reported in younger, healthy males aged 12 to 29 years old.[2] Symptoms usually occur 3 to 5 days after administration of the second dose of vaccine, suggesting an immune-mediated mechanism.[3,4] Most patients present with chest pain (100%), muscle aches, fatigue or fever (63%) with elevated troponin levels (100%), as well as elevated blood biomarkers of inflammation such as C-reactive protein.[5]

Workup of mRNA COVID-19 vaccine-induced pericarditis and myocarditis

The workup should include detailed clinical history-taking, a 12-lead electrocardiogram (ECG) and blood biomarkers, particularly high-sensitivity cardiac troponin T/I in accordance with the current recommended clinical practice guidelines for patients presenting with acute chest pain.[6] A history of symptoms suggestive of recent infection or preceding strenuous activity should be sought. Chest discomfort may also be pleuritic or positional in nature, worsening with lying down and improving with sitting up. Clinical examination should assess for fever, haemodynamic instability, signs of fluid overload and also for the presence of a pericardial rub. The diagnosis of myocarditis can be challenging as it may mimic acute myocardial infarction and also Takotsubo syndrome in its clinical presentation, and associated ECG abnormalities and blood biomarkers. In some patients, particularly those with co-existing cardiovascular risk factors, exclusion of acute coronary syndrome by invasive coronary angiography or computed tomography coronary angiography may be necessary after consideration of a pre-test probability for ischaemic heart disease. In cases with normal troponin levels and a normal ECG at presentation, isolated pericarditis should also be considered. In patients with myocarditis after vaccination with the first dose of the mRNA COVID-19 vaccine, assessment of serological evidence for prior SARS-CoV-2 infection (determination of SARS-CoV-2-Nucleocapsid-IgG) can be considered in line with the postulated immune-mediated mechanism for vaccine-associated pericarditis and myocarditis.

87% of the affected patients present with ECG abnormalities suggestive of pericarditis and myocarditis.[2] ECG abnormalities suggestive of

pericarditis and myocarditis can include widespread concave ST elevation and PR depression. As per current cardiac magnetic resonance imaging (CMR) recommendations for the workup of myocarditis, further assessment of the cardiac structure and function with echocardiography and the performance of CMR for assessment of pericardial and myocardial inflammation and tissue damage should be considered.[7] Acute myocarditis may result in regional or global contractile dysfunction. There can also be extensive tissue injury reflected by subepicardial late gadolinium enhancement on CMR with comparably minimal effect on cardiac ventricular contractility. This is because endocardial myocytes, which are key contributors to ventricular contractile function, are usually spared in myocarditis.[8]

Management of mRNA COVID-19 vaccine-induced pericarditis and myocarditis

In the management of mRNA COVID-19 vaccine-induced pericarditis and myocarditis, chest pain can be symptomatically treated with paracetamol or non-steroidal anti-Inflammatory drugs (NSAIDs) as required.[10] Heart failure treatment such as with angiotensin converting enzyme (ACE) inhibitors and beta blockers can be considered,[9] particularly in cases with ventricular contractile dysfunction. Its indication should be re-evaluated during follow-up review. In cases with presumed pericardial inflammation, immunomodulatory therapy such as colchicine can be considered. The use of intravenous globulins or corticosteroids should be individually assessed in severe cases.[10] The clinical course of mRNA vaccine-associated myocarditis has been mostly benign without significant arrhythmias and with rapid complete spontaneous recovery.[2] So far, only a few cases in older adults have been reported with varying outcomes depending on other co-morbid conditions,[2] in addition to two cases with a fulminant course.[11]

Real world data with regards to mRNA COVID-19 vaccine-induced myocarditis incidence

Based on real world data from Singapore, Israel and the United States regarding vaccine-associated cardiac inflammation, there seems to be a slightly higher than expected occurrence of myocardial inflammation in male adolescents and younger adults. However, myocarditis occurring after mRNA vaccination is still very rare.[10] In a large retrospective case series involving members of the US military, 23 male patients with a median age of 25 years were diagnosed with vaccine-associated myocarditis out of more than 2.8 million doses of mRNA COVID-19 vaccines administered. Eight of these 23 patients had CMR results for diagnosis and none of them had histopathological evidence, leading to eventual diagnosis of probable myocarditis.[12]

Safety of mRNA COVID-19 vaccine with regards to myocarditis

A recently published Israeli study described risks for adverse events after mRNA vaccine in comparison with the risks of the same adverse events after infection with SARS-CoV-2.[13] The risk ratio of myocarditis was estimated to increase by a factor of 3.2 after receiving mRNA vaccine, with 1 - 5 events per 100,000 persons.[13] In comparison, the risk of myocarditis was increased by a factor of 18.3 after SARS-COV-2 infection. In addition, the risk for multiple other serious adverse events apart from myocarditis was substantially higher after SARS-COV-2 infection than after vaccination.[13] The benefit of COVID-19 mRNA vaccination in terms of prevented hospitalisations compared with its risk of vaccine-associated myocarditis seems to clearly be in favour of vaccination, especially with increasing age.

Local situation

As at 31 October 2021, HSA has received 86 AE reports of myocarditis and pericarditis following more than 9.9 million doses of mRNA vaccines administered in Singapore. The risk is observed to be highest in younger males aged 30 years and below (incidence rate of 3.69 per 100,000 doses administered) compared to females from the same age group (incidence rate of 0.47 per 100,000 doses administered). Of the 49 cases which occurred in individuals aged 30 years and below, 44 (90%) had occurred in males. It is observed that the risk in females was highest in those aged 20 to 49 years old with an incidence rate of 0.63 per 100,000 doses. All the patients were reported to have recovered or are recovering.

The risk of myocarditis and pericarditis is also observed to be higher with Dose 2 of the vaccine, comprising 64% of the reported cases. The incidence rates of myocarditis and pericarditis following Dose 2 of the vaccine are 5.8 per 100,000 doses administered in those aged 12 to 19 years old, 2.0 per 100,000 doses administered in those aged 20 to 29 years old, and 0.61 per 100,000 doses administered in those aged 30 years and above.

AE CASE IN FOCUS 2: TEST YOURSELF

A 20-year-old female presented to the Emergency Department with coughing and two episodes of haemoptysis. The blood stain from haemoptysis was the size of a 5-cent coin, with small blood clots that stained her mask. She also reported haemoptysis the day before and 2 weeks prior.

During history taking, she revealed that she had been using flavoured electronic cigarettes (e-cigarettes) regularly over the past five years. She reported using e-cigarettes daily, with each filter lasting around 1 to 2 weeks. During those acute episodes of haemoptysis, she would stop using them but would then resume vaping again after the episodes had resolved.

Her medical history includes a history of recurrent trivial haemoptysis since 2017. The investigation previously done included acid-fast bacilli culture tests in 2017 and 2019, of which the results were negative. Otolaryngology review in 2017 and 2019 also did not reveal any upper airway cause and an esophageal gastroduodenoscopy performed in 2018 was normal. A computed tomography (CT) scan of the thorax in 2020 showed minor linear atelectasis. No focal consolidation or suspicious lung lesions were detected.

She was also a cigarette smoker of three pack-years. She had previously worked as a general cleaner but denied heavy exposure to smoke, fumes, chemicals or dust. She had no personal or family history of tuberculosis, lung cancer, asthma or any airway diseases. She was also not taking aspirin, anticoagulant or any health supplement.

Her clinical examination was unremarkable. Her admitting chest X-ray showed mild lower zones infiltrates (Figure 1).

Question: What could have caused the patient's cough with haemoptysis?

HSA would like to thank Dr. Scott Wong Wei Gen, Internal Medicine Resident, Dr. Clare Fong, Senior Resident and Dr. Chua Ai Ping, Senior Consultant, Division of Respiratory Medicine, Department of Medicine, JurongHealth Campus, National University Health System for contributing this article.

Answers can be found on page 8

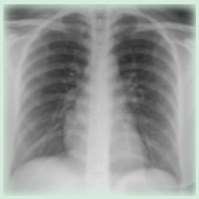


Figure 1. Chest X-ray on hospital admission

Conclusion

Healthcare professionals are required to report all suspected serious AEs associated with COVID-19 vaccines to HSA. The reports will allow better computation of the frequency of AEs in Singapore and potentially in subgroups of individuals, for the monitoring of the safety of mRNA vaccines to ensure that their benefits continue to outweigh their risks in a pandemic.

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ANSWERS TO AE CASE IN FOCUS 2: TEST YOURSELF

The patient was diagnosed with e-cigarette or vaping product use associated lung injury (EVALI).

Case Progress

We present the details of the case investigation that led to the diagnosis. Her laboratory tests did not reveal neutrophilia or eosinophilia, and her haemoglobin level, coagulation profile and renal function were normal. Her serum autoimmune markers including anti-nuclear cytoplasmic antibody, anti-nuclear antibody, rheumatoid factor and anti-glomerular basement membrane were found to be negative. She was also tested to be negative for COVID-19 infection. The results for her sputum microbiology testing (smear, molecular and cultures) for mycobacterium tuberculosis were negative. Computed Tomography Pulmonary Angiogram (CTPA) which was performed 5 days following her last episode of haemoptysis showed no filling defects in the arteries, and no consolidation, collapse, or any suspicious masses. She also underwent a bronchoscopic airway inspection which did not reveal any localised bleeding source or endobronchial lesion.

The patient did not have further episodes of haemoptysis during her short hospitalisation stay following symptomatic management of her condition and was discharged well. Prior to that, she was informed of the possibility of EVALI and was advised against using e-cigarettes or any vaping products. Upon a 3-month post-discharge follow-up call, she reported that she was well and had abstained from using e-cigarettes and reported no further episodes of haemoptysis.

About E-cigarette or Vaping Product Use Associated Lung Injury (EVALI)

E-cigarettes and other types of electronic vaporisers (e-vaporisers) are battery-operated devices which heat a solution or e-liquid and produces a vapour which is inhaled by the user. The ingredients of the e-liquid vary widely and may include nicotine, propylene glycol, glycerin, and flavouring agents.[1] The purchase, use and possession of e-cigarettes or e-vaporisers has been prohibited since February 2018 in Singapore under the Tobacco (Control of Advertisements and Sale) Act.[2] Information pertaining to the prohibition of harmful and imitation tobacco products in Singapore is available on the HSA website and more details about the harms of e-cigarettes and e-vaporisers can be found in this HealthHub article.

EVALI is a form of an acute lung injury arising from vaping-induced pulmonary inflammation, with pathologic findings of acute fibrinous pneumonitis, diffuse alveolar damage, or organising pneumonia, usually bronchiolocentric and accompanied by bronchiolitis.[3] The pathogenesis is not known and there may be more than one disease process and mechanism of injury. The key risk factor is the use of an e-cigarette or a similar product in the past 90 days. The United States (US) Centers for Disease Control and Prevention defines a confirmed case of vaping-associated lung injury by the use of an e-cigarette 90 days before symptom onset, pulmonary infiltrates on chest imaging, absence of viral, bacterial, or fungal infection and no evidence of a cardiac or rheumatologic cause.

The Health Sciences Authority has observed an increase in the number of seized electronic vaporisers since 2019. From 1 January 2018 to 30 September 2021, HSA has prosecuted 63 persons for selling e-vaporisers and their related components.[4] In the US, EVALI is an emerging national emergency where there is a growing number of cases in patients under the age of thirty-five years old who vape, and over 2,800 cases of EVALI and 68 deaths have been reported as of February 2020.[5,6]

In a systematic review of EVALI, patients commonly present with respiratory symptoms such as dyspnoea, chest congestion and cough, along with gastrointestinal symptoms and fever around one week after the start of vaping.[7] Haemoptysis is a less common presentation with around 10% of patients being affected.[7] In a case series of 98 patients in the US, hypoxaemia on hospital admission (O2 saturations 89-94% on RA) was present in 33% of the patients and 25% of them had oxygen saturation of less than 89%.[8]

There is no single specific test to diagnose EVALI. Diagnosis is based on the history of vaping product use and excluding other well-established aetiologies such as infection, neoplasm, autoimmune, vascular, and other pulmonary pathology. Computed tomography (CT) scan of the thorax may reveal diffuse ground glass opacities, but there is no specific pattern of location of radiographic abnormality.[7,8] Flexible bronchoscopy with bronchoalveolar lavage (BAL) can rule out other causes of non-resolving or progressive pneumonitis. Cell counts may show an increase in neutrophils, and presence of foamy lipid laden-macrophages in alveolar spaces with Oil-Red-O lipid stain but are both non-sensitive and non-specific findings.[8] Likewise, histology of the lung tissues often shows non-specific features of acute lung injury. Further avoidance of the vaping product and supportive treatment remains key in the management of EVALI. A trial of steroids may be considered in more severe cases.

EVALI is an uncommon cause of recurrent haemoptysis and remains a diagnosis of exclusion. It is important that healthcare professionals maintain a high index of suspicion for EVALI in patients who present with haemoptysis or respiratory symptoms, especially in the context of a current or past history of e-cigarette use or vaping.[9] A careful medical history-taking would help in the accurate diagnosis of EVALI. It is also important that patients completely stop using e-cigarette or vaping to achieve good clinical outcomes.

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Please send your enquiries, comments and suggestions to:

Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way, #11-01,
Helios, Singapore 138667

Tel : (65) 6866 1111

Website: http://www.hsa.gov.sg
Email: HSA_productsafety@hsa.gov.sg