TRANSCRIPT

S3.E4 – Cutaneous Drug Reactions

Dr Blake Mumford: The battle against polypharmacy or the use of a large number of drugs, of the action of which we know little, yet we put them into bodies of the action of which we know less has not been fought to a finish.

Welcome to *Spot Diagnosis*, a podcast about all things dermatological brought to you by the Skin Health Institute in Melbourne, Australia. I am Dr Blake Mumford, Education and Research Fellow at the Institute.

Dr Anneliese Willems: And I am Dr Anneliese Willems. I'm a GP, medical educator, and Research Fellow at the Skin Health Institute. Blake and I are your co-hosts today. That opening quote is attributed to Sir William Osler, a famous physician from the early 20th century, and is one of his many warnings about polypharmacy. The topic of today's episode is drug eruptions.

As a reminder for our GP listeners, *Spot Diagnosis* has been accredited with RACGP and ACRRM. There is one CPD point per episode so approximately 9 to 10 points per season. All you need to do is to subscribe to the podcast, listen to all the episodes, and fill in a brief evaluation form on spotdiagnosis.org.au. Repeat, that was spotdiagnosis.org.au.

Blake: Our guest today is Dr Michelle Goh, a Consultant Dermatologist at the Institute, who happens to share the record for the most guest appearances on the *Spot Diagnosis* podcast, which I assure you is a great honour. Welcome back, Michelle.

Dr Michelle Goh: Thanks very much for having me back.

Blake: Now, Michelle has a particular interest in cutaneous drug eruptions. Could you tell us a bit about your work with adverse drug eruptions, Michelle?

Michelle: I am a member of the Adverse Drug Reaction Committees at the Alfred and Austin Hospitals. It is a multidisciplinary group that reviews cases of adverse drug reactions. We review the clinical presentation of the possible reaction, then we review the medication timeline leading up to the event, and try to attribute causality and give advice as to further future medication use. There is a fair bit of detailed detective work required in correlating all the necessary information. Thanks to our amazing pharmacists.

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Anneliese: And Michelle, can you share with us an interesting case of a drug eruption that you've come across?

Michelle: I remember a patient who was admitted for investigation of high fevers and a rash, who was treated with intravenous antibiotics for presumed sepsis. It wasn't until the second admission and after extensive investigations failing to reveal any infection, that the penny dropped that this was indeed a hypersensitivity reaction to a medication that was started six weeks prior.

Blake: What was the drug in the end, Michelle?

Michelle: The culprit turned out to be sulfasalazine for her rheumatoid arthritis.

Blake: That's very interesting. I think this is an important lesson to always consider drug eruptions as a potential cause for a rash. Can we start by exploring why drug eruptions occur?

Michelle: There are different mechanisms in which a drug can elicit an immune response and cause a drug eruption. One of these is when a drug-hapten complex is formed. This occurs when a drug is bound by a protein in the body, for example, penicillin binding with albumin. This binding causes a unique antigen signature that stimulates a T-cell or antibody response. The second mechanism involves the drug or metabolite interacting directly with T-cell receptors or HLA molecules leading to a T-cell stimulation.

Anneliese: And how common are drug eruptions?

Michelle: Drug eruptions are very common. It is said that drug hypersensitivity concern more than 7% of the general population. These drug eruptions will obviously be of varying severity. Not everyone will have a severe response.

Blake: How do we classify drug eruptions into groups?

Michelle: Drug eruptions are classified according to the underlying immunological mechanism. Type I and Type IV are the vast majority of drug reactions, and we will focus on these today. Type I reactions are the immediate IgE-mediated reactions.

Blake: So that's like, urticaria, angioedema, and anaphylaxis. Is that right?

Michelle: Yes, that's correct.

Blake: And, what about the Type IV reactions?

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Michelle: So Type IV reactions are the delayed-type hypersensitivity that is T cell-mediated immunological mechanism by which the large majority of drug eruptions occur such as maculopapular eruptions.

Anneliese: It sounds like drug eruptions can be quite diverse. Not all drug reactions are maculopapular or urticarial. Some can be very serious and life-threatening.

Blake: Indeed. There is a cool-sounding acronym called SCARs, or severe cutaneous adverse reactions. What are the SCARs that GPs and hospital medical staff should be aware of?

Michelle: The acronym says it all S-C-A-R, SCAR, stands for Severe Cutaneous Adverse Reactions. It has potentially significant morbidity and sometimes, unfortunately, also mortality. The four major SCARs are number one, DRESS syndrome, which stands for drug rash with eosinophilia and systemic symptoms, also known as drug hypersensitivity syndrome. Number two and three are the SJS, Stevens-Johnson Syndrome, and TEN, toxic epidermal necrolysis spectrum. And number four is A-G-E-P, AGEP, which stands for acute generalised exanthematous pustulosis.

Anneliese: What signs should I look for that SCAR, or severe cutaneous adverse reaction, might have occurred?

Michelle: An unwell patient with fever or any internal organ involvement.

Anneliese: And what about the rash itself?

Michelle: Any skin burning or pain, a violaceous or purple hue to the colour of the rash, or dusky grayish colour indicating skin necrosis, vesicles, blisters, erosions, and skin loss or pustules.

Blake: And what about mucosal involvement, Michelle? I heard that might be an important indicator.

Michelle: It is important to look for and manage any eye, mouth, or genital involvement.

Blake: It's time for our first **skin tip**. You should consider the possibility of a SCAR if the patient is unwell, has a fever, or if there is evidence of internal organ involvement. The skin signs to watch out for include blisters, pustules, vesicles, or evidence of mucosal involvement.

Anneliese: Michelle, I'm curious. What is the most common SCAR?

Michelle: The most common SCAR is DRESS syndrome, which is an acronym that stands for drug rash with eosinophilia and systemic symptoms. It is a potentially life-threatening drug eruption

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which manifests as a usually widespread macular and papular rash accompanied by fever and facial swelling. These patients also usually have an eosinophilia and abnormal liver function tests.

Blake: It sounds like, those are all signs of a SCAR, Michelle. The fever, eosinophilia, and abnormal liver function tests.

Michelle: Yes, the internal organ involvement.

Anneliese: It sounds like these patients can be quite unwell. Do they all need urgent referral for hospital assessment?

Michelle: Well, like all things in medicine, DRESS can also be in a spectrum from mild maculopapular eruption with mild eosinophilia and liver derangement to the severe end of the spectrum with multiple internal organ manifestations. So, no, mild cases do not need hospital management.

Blake: One of the commonly implicated drugs? It's definitely got to be antibiotics, right?

Michelle: Yes. antibiotics usually beta-lactams but also anticonvulsants, allopurinol, and sulfonamides such as sulfasalazine and sulfamethoxazole.

Anneliese: Can you describe a typical case of DRESS syndrome that you would see in the hospital setting?

Michelle: I remember a patient who had been started on an anticonvulsant following neurosurgery. Three to four weeks later, he presented with fever, facial swelling, a widespread maculopapular rash, abnormal liver function tests, and eosinophilia.

Anneliese: And how do we treat DRESS?

Michelle: The first step is to exclude other possible diagnoses such as an infectious exanthem. If you are happy that this is DRESS, then you need to identify the culprit drug and stop it. In severe cases, we often use systemic corticosteroids.

Blake: Stevens-Johnson Syndrome, SJS, and toxic epidermal necrolysis, TEN, are the most feared SCARs. Can you tell us about this, Michelle?

Michelle: SJS and TEN are severe drug eruptions that can result in mortality and should be considered a medical emergency. These patients present unwell and in pain. They have severe mucosal involvement with crusted lips, painful conjunctivitis, mouth ulceration, and large areas of blistered raw skin.

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SJS and TEN are the same disease process differing only in the extent of skin involvement. The blistering rash is due to epidermal necrosis, which ultimately leads to the detachment of the epidermis from the dermis. These patients must be handled delicately, and ideally managed in an intensive care burns unit.

Blake: Why do these patients need to be managed in a burns unit?

Michelle: The skin loss is similar to a second-degree burn, and the mortality of SJS and TEN is, in some ways, proportional to the amount of skin affected. The complications that need to be managed in SJS and TEN are like those seen in severe burns, which is fluid and electrolyte, pain and infection sepsis management. These patients are usually managed in an intensive care unit to limit these complications and to facilitate careful daily wound care and pain management.

Anneliese: Which drugs are commonly implicated?

Michelle: So the common culprits are the same as those that cause DRESS; antibiotics, anticonvulsants, allopurinol.

Anneliese: Can you tell us about a patient with TEN that you have managed?

Michelle: Just this year, I looked after a lady in her 30s who had started four drugs simultaneously for an autoimmune condition. She presented with an itchy face which he thought was related to a new cosmetic product, but later developed a fever and so presented to the emergency department. She then developed mouth ulceration and blisters around her mouth. In the end, she progressed to 90% body surface area skin blistering, and she was managed at the Alfred Hospital Burns Unit. She recovered and the drug culprit, in the end, was sulfamethoxazole. In fact, this lady actually wrote about her experience of TEN in a series of blog posts, which makes for a very interesting and informative read.

Blake: Thanks for sharing that story, Michelle, I'll second that recommendation. The blog is available at survivingtens.wordpress.com, and we'll include a link on our website spotdiagnosis.org.

Anneliese: On that note, I think it's time for our second **skin tip** of today. SJS/TEN is a medical emergency. Any patients presenting with SJS or TEN should be transferred to hospital as soon as possible.

Blake: Moving on to acute generalised exanthematous pustulosis. It is a typically named dermatological disease, beautifully descriptive, but a bit of a mouthful. What is AGEP or A-G-E-P?

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Michelle: A-G-E-P or AGEP is a rapidly evolving eruption where patients present with generalised tiny pustules overlying a background of red skin. They are often unwell and have a fever. This is an uncommon SCAR.

Blake: It sounds like it could be quite similar in appearance to generalised pustular psoriasis.

Michelle: Yes, AGEP and generalised pustular psoriasis can look very similar clinically. It can be difficult to differentiate between these two. The biggest clue is a preceding history of psoriasis versus a recently commenced drug. And a good history is critical to differentiate the two.

Anneliese: Which drugs are usually implicated in AGEP? Is that the same old friends that cause DRESS, SJS and TEN?

Michelle: Actually, unlike the other SCARs, in AGEP it's usually antibiotics.

Blake: What's your approach for identifying culprit drugs for SCARs?

Michelle: Take a careful drug timeline, not only prescribed oral medications, but also over-the-counter products such as painkillers, cough and cold medications, vitamins and herbal supplements. And not only oral medications, but topical products such as eyedrops.

Blake: And what's your approach if the patient's taking like lots of medications? Do you just stop everything or do you have some kind of selective process for it?

Michelle: If there's any very suspected drugs, that they are definitely to be stopped. But if there are multiple potential culprits, any drug that is not absolutely essential will be temporarily ceased, at least. Patients don't always know what exactly they're taking and medication lists may be out of date, so it's important to get drug history from multiple sources.

Blake: Right, okay, and does the time interval between exposure and onset of the rash help in any way?

Michelle: So DRESS classically starts between two to six weeks. The latency is slightly shorter for SJS and TEN, at seven to 21 days, and AGEP has the shortest time latency, usually within a matter of days. Although, in general, any new drugs started within the last two, even up to three months, is potentially suspect. It is also important to be aware that if a patient has previously been sensitised to a drug, a SCAR can start within hours of re-exposure.

Anneliese: Michelle, what information would you want to see on a GP patient referral for a suspected SCAR?

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Michelle: A timeline of the clinical presentation, with the dates and time when the fever, or sore throat, or rash were first noted, and the drug timeline. A complete medication list and previous allergy or drug reaction history.

Blake: It's time for another **skin tip**. When attempting to identify a culprit drug, it is important to ask about drug exposures that have occurred in the last few weeks and not just the last few days.

Blake: When investigating these patients, Michelle, is there a role for patch testing or skin prick testing to identify the causative drug?

Michelle: Diagnostic skin testing is available, but has a limited role at this stage. Skin testing must be done in conjunction with a thorough history of drug exposure and phenotypic classification of the reaction. Skin prick testing is most useful for type 1 IgE-mediated reactions, whereas, patch testing can be useful for AGEP and fixed drug eruption. However, these tests have low sensitivity and their role is currently being studied.

Anneliese: Is skin testing useful for investigating cross-reactivity? For example, if a patient is allergic to penicillin, whether they're also allergic to cephalosporins.

Michelle: Yes, skin testing can also be used to assess for drugs that may potentially cross-react. As you say penicillins and cephalosporins are potentially cross-reactive. In general, skin testing can be used to identify whether the reaction is drug-specific or generalisable across a class. It can also be used to de-label an allergy, which is considered low risk. In such cases, a negative skin test result permits a supervised drug challenge.

Blake: Michelle, I get the impression that not everyone who has a drug eruption needs to be referred for these tests. Is that right?

Michelle: Not everybody. It depends on the level of risks and importance to find out which drug is the culprit.

Blake: I see, okay. We mentioned at the start that the immune system is involved in drug eruptions, but genetics can also play a role. Michelle, can you give us some examples?

Michelle: Yes, this field of immune pharmacogenomics is an expanding one and the way of the future. We are starting to discover that some of these immunological drug reactions are, in fact, predictable by genetics. Abacavir was the first drug in which hypersensitivity was found to be associated with a specific HLA type. This association is so strong that pretreatment testing is a clinical standard. HLA associations have now also been found for allopurinol and carbamazepine in Han Chinese.

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Blake: Now that we've discussed the SCARs, let's talk about some of the more benign drug eruptions, the most common of which is the infamous maculopapular drug eruption. There is a meme video online of someone pretending to be a Dermatology Registrar and complaining that the only referral he ever receives is for a maculopapular drug eruption. Michelle, what is the infamous maculopapular drug eruption, and how does it present?

Michelle: As per its description label, it is both macular, that is flat, as well as papular, which is raised. It's usually smooth, and thus, can be described to be urticarial. It is usually a red, itchy rash, which predominantly affects the trunk initially, and then spreads distally.

Blake: It sounds like maculopapular rash is what some doctors say when they don't know the difference between a macule and a papule. What are the commonest causes of a maculopapular drug eruption?

Michelle: Most drug classes can cause a maculopapular drug reaction. However, the highest risk drugs are our old friends from before, antibiotics and anticonvulsants.

Blake: Do Dermatologists get triggered when people refer maculopapular rash? Like do you ever believe anyone when they say it's a maculopaupular rash?

Michelle: But it's usually real, because everyone's got a maculopapular rash.

Blake: True, true.

Michelle: It's got to be something.

Anneliese: And what do we do for treatment?

Michelle: Again, stopping the culprit drug is the most important treatment. For symptom relief of non-severe maculopapular eruption, management of the itch with topical corticosteroids, simple moisturisers, and oral antihistamines can help. Oral prednisolone is sometimes used if the eruption is severe or causing significant distress. More importantly, the patient should be monitored for any clinical features indicating an evolution into a more severe adverse reaction, such as a SCAR that we've talked about before.

Anneliese: I think it's time for another **skin tip**. Maculopapular drug eruptions, if they're mild, can be treated by simply stopping the culprit drug and simple measures such as antihistamines and topical corticosteroids.

Anneliese: Shifting to something a little bit different, Michelle, something that health professionals, in general, could improve is allergy labeling. Often a patient has a vague and distant memory of a

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penicillin allergy. They can't remember what happened or when, but they've been told by the relative or a doctor to avoid penicillin in the future. Why is this the problem, Michelle?

Michelle: There are quite a few people with a label of penicillin allergy, and some of these are real and serious like anaphylaxis, in whom the entire class of beta-lactams, meaning all penicillins and cephalosporins should be avoided until further allergy assessment. However, more commonly, patients come with a vague and distant history of penicillin allergy as you say. A typical story is: "My mother said to me when I was still a child that I have a penicillin allergy, but I don't know what happened." Many of these remote childhood vague penicillin allergies can effectively be de-labeled with testing and challenge in a hospital setting. This is important as it potentially allows entire classes of antibiotics to be used safely to treat infections.

Blake: This presumably has benefits at a public health level as well. A lot of the alternatives to penicillins and cephalosporins are often broad-spectrum and promote antibiotic resistance.

Michelle: Yes, exactly. This is an important part of good antimicrobial stewardship.

Blake: During one of my first cover shifts, as a new intern, I was called to see a patient who has developed an itchy rash which turned out to be urticaria. I checked the drug chart and a penicillin had recently been started, at which point, I panicked and called my boss. Why does urticaria occur?

Michelle: Urticaria occurs due to a drug-specific IgE leading to mast cell degranulation of histamine and other mediators. It is very common, much more common than a SCAR.

The treatment is to stop the drug and manage the urticaria with anti-histamines. So no need to panic, Blake.

Anneliese: Now it's time to challenge your clinical acumen, Michelle, to prove that you are worthy of the *Spot Diagnosis* hot seat. We're going to give you three clinical scenarios, and in each case, you must correctly diagnose and treat the case.

Our first clinical case. A 22-year-old female attends for review two days after seeing your colleague, with query HSV-induced gingivostomatitis, which had been managed conservatively. She became unwell four days ago with a flu-like prodrome associated with ulcers to her lips and mouth. Her history is unremarkable except for a UTI, which was treated two weeks ago with trimethoprim and sulfamethoxazole.

On examination, her temperature is 39.2°C. She is miserable. Her eyes are red and slightly painful, and she has extensive ulceration to the oral mucosa in addition to new ulceration to also the vulva and perianal mucosa. She also has a widespread erythematous rash. Michelle, how would you approach this case?

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Michelle: So the major diagnostic challenge here is determining whether this is an infection or a SCAR, likely SJS/TEN spectrum to trimethoprim or sulfamethoxazole, which should be ceased. She is very unwell, so she should present to the emergency department and undergo multidisciplinary team assessment and treatment by a Dermatologist, Ophthalmology, Ear, Nose and Throat, and Gynecology. She should have a skin biopsy, swabs for herpes virus, bacteria and candida. She should be admitted for pain relief, regular skin and mucosal care, and careful fluid balance. If she progresses, she may require management in an ICU burns unit setting.

Blake: How are you holding up, Michelle? You still feeling good?

Michelle: All good.

Blake: Very good. All right.

Blake: The 28-year-old gentleman presents to you in a disgruntled state, "I reckon I have the measles, doc" He declares incredulously. It all started a week after he started taking amoxicillin-clavulanic acid for presumed lower respiratory tract infection. Indeed, your finely honed examination skills detect a widespread symmetrical maculopapular eruption. You astutely exclude facial edema, pustules, vesicles, and mucous membrane involvement. Does he really have the measles, Michelle?

Michelle: He's unlikely to have measles in this day and age in Australia, but I guess it's always possible. We need to know his vaccination status and exposure history. It's likely we're dealing with a maculopapular drug eruption to amoxicillin-clavulanic acid. In this case, I think we can manage him by simply withdrawing the drug, use of topical corticosteroids and oral anti-histamines, with close clinical follow-up review. We could consider an alternative antibiotic if needed.

Anneliese: and for your final clinical scenario.

Anneliese: A 30-year-old male has been commenced on phenytoin for management of his epilepsy. Two weeks later, he comes to you and is almost unrecognisable. His face is swollen, and he has a widespread of fine papular eruption affecting his face, upper trunk, and extremities. You know there is not much in the way of mucosal involvement, but he is febrile at 38 degrees.

Michelle: This most likely sounds like DRESS syndrome, given the fever, facial swelling, and widespread rash in the context of a new drug two weeks ago. I would refer this man to hospital and cease the medication and any other suspect, unnecessary drugs. I would do some basic blood investigations, like the full blood examination, renal function, liver function. I would then consider commencing topical and systemic corticosteroids for symptom relief.

Blake: Well, Michelle, I think that's a perfect three out of three. Congratulations.

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Michelle: Thank you.

Blake: That concludes our episode on drug eruptions. We hope this podcast scores a 10 out of 10. Get it? 10 out of Toxic Epidermal Necrolysis.

Anneliese: Thank you, Michelle, for your time, and sharing your expertise with us.

Michelle: Thank you for having me.

Blake: We'd also like to thank our Producer, Jo Coughlin, and our Director, Associate Professor Alvin Chong at the Skin Health Institute.

Anneliese: We hope you have enjoyed this episode of *Spot Diagnosis*. Remember, these podcasts are not meant to replace medical advice. If you have a skin condition that requires attention, we strongly encourage you to see your medical practitioner.

Blake: For listeners who want more information on this subject, a transcript of this episode and links to other resources can be found on our website, spotdiagnosis.org.au. That's spotdiagnosis.org.au.

Anneliese: Please share *Spot Diagnosis* with your friends and colleagues. Rate and review us. Let us know what you think. We would really appreciate your feedback and any suggestions.

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