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Skin Rash In a Patient Using Antiepileptic Medications, What It Could Be?

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This is an original work based on a clinical condition for a patient that was admitted to the hospital.

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"Informed consent was obtained from the patient's next of kin (his wife) for publication of this case report and accompanying figures."

Skin Rash In a Patient Using Antiepileptic Medications, What It Could Be?

Learning points:

- Assessment of a rash is not different to other medical assessments. It relies on history and examination and it also rests with pattern recognition.
- We should not assume and consider that a rash, in a patient treated with rash provoking medications, is definitely because of that medication.
- Systematic approach to a rash should lead to appropriate diagnosis and treatment.

Abstract

Introduction: Rash is one of the commonest presentations that doctors can be asked to review. Studying this case strengthens the understanding about how to review a patient with rash and how to formalise differential diagnosis based on the clinical condition. This is an educational article that seeks to improve medical students understanding and clinical applications around rashes and to establish an approach that will differentiate between medications evoked rash and rash provoked by other causes.

Case overview: This case study will provide a systemic approach when evaluating a skin rash in a patient, especially in a person who cannot communicate and who has been exposed to rash provoking medications.

Discussion overview: Antiepileptic medications are known to evoke rash. It is important to take that in consideration when evaluating rashes in patients who are using those medications; however we should keep in mind that there are other conditions that can be the cause.

Introduction

Skin diseases are common in patients presenting to general practice or in patients who are admitted to the hospitals. This case presents a 56 years old gentleman who has a complex neurological condition and and he was found to have skin rash whilst admitted to neurology ward. It is very common to be asked to review patients with new rash or skin condition while they are admitted to the hospital for another reason. This case highlights the importance of differentiating between de novo health problems and problems related to chronic health conditions.

Case:

History

GM is a 56-year-old nonverbal and fully dependent man who was admitted to the hospital from a nursing home because of multiple seizures. His comorbidities included: advanced neurodegenerative disease, Hereditary Endotheliopathy, Retinopathy, Nephropathy and Stroke (HERNS) -a rare autosomal dominant condition that affects the vascular

endothelium of the brain, retina, and kidneys. This was further complicated by vascular dementia, quadriplegia, epilepsy, diabetes insipidus, hypertension and hyperlipdemia.

His regular medications were: dexamethasone 1mg mane, phenytoin 430mg mane and 130mg nocte, thyroxine 50mcg mane, levetiracetam 1g three times daily, lacosamide 150mg twice daily, valproate 1200mg mane, 1000mg mid-day and 1200mg nocte, enoxaparin 40mg daily, metoclopramide 10mg as needed, midazolam 2.5mg as needed.

He presented to emergency department following three tonic-clonic seizures with reduced level of consciousness. Antiepileptic medications (AEM) levels were checked, valproate level was 26 mg/L (therapeutic level 50-100mg/L) and he was loaded with 1 gram of valproate by emergency department staff.

In the emergency department, he received intravenous midazolam 1mg to terminate a further seizure and he had no further seizure activity thereafter. He received ondansetron for vomiting; ampicillin and gentamicin were prescribed for urinary tract infection and then were changed to tazocin as urine culture grew pseudomonas aeruginosa. He was then admitted under the care of neurology team.

The following day, nursing staff noticed a rash on his back, between his scapulae, and multiple smaller lesions on the right hip which had not been noticed at the time of admission.

As he could not give a history, collateral history was taken from his wife and the registered nurse who looked after him in the nursing home. The registered nurse stated that the rash was not noticed prior to his admission to the hospital.

There was no recent change in medications including over-the-counter (OTC) medications; no change in regular bed sheets, clothes, cleaning agents. There was no history of insect bites, no similar presentations in the household and no history of recent travel.

He had a localised red rash over the left side of the chest a few weeks prior to this presentation for which he was treated with hydrocortisone 1% w/w and clotrimazole 1% w/w cream by his general practitioner with resolution of the rash.

His wife was not aware of the current rash and stated that he does not have a history of allergy, eczema or asthma.

A consultation for his rash was sought from the neurology team as he was on numerous antiepileptic medications, known to evoke rash.

Assessment

His vital signs were stable. The lesions were well demarcated, annular, advancing centrifugally from a core, leaving a central clearing and mild residual scaling.

There was a ~10X10cm erythematous patch with active borders and central clearance on the back, between the scapulae. Multiple similar smaller lesions were noted over the right hip (Figure 1). The rash was not generalised and there was no involvement of mucous membrane. It was unlikely that the rash was pruritic, as the patient was not in distress and there were no scratching marks present.

Results

Full blood counts were normal, including normal eosinophil count. C-reactive protein (CRP) was 312 mg/L (normal range < 4.9 mg/L) on presentation, likely secondary to his urinary tract infection, and it was down trending with antibiotic therapy.

Skin scraping culture was positive for *trichophyton rubrum*.

Differential diagnosis

One of the differential diagnoses for the rash in this patient was the cutaneous side effects of antiepileptic medications or a reaction to medications that were prescribed on admission. However, the rash appearance favoured fungal infection for which he was treated.

Management

Terbinfine hydrochloride 1% twice daily was commenced and the patient was treated as having tinea corporis infection, with skin scraping taken prior to commencing treatment.

Discussion

Patients with skin conditions comprise 17% of general practice consultations in Australia and rash accounts for 2.5% of the total presentation to general practice[1, 2]. Common skin condition presentations to general practice include dermatitis, acne, psoriasis and skin infections[1].

Skin rashes can be induced by certain medications. It is not uncommon to review patients who present with skin rashes along with having other complex comorbidities for which they are taking medications that can cause skin eruption. The diagnosis of drug induced skin eruption can sometimes be very difficult to establish, as a cutaneous drug eruption can closely mimic other common skin diseases[3].

Types of rash can sometimes be difficult to diagnose due to the varying morphological forms that it can present. Many conditions may produce similar rash, some conditions may present with atypical appearance of rashes and some rashes may have altered appearance after starting certain medications or with development of secondary bacterial infections. The patient may be unable to offer adequate history pertaining to the rash. Furthermore, the patients and carers may adopt a trial of medications or herbal remedies before seeking medical advice; especially within the context of uncertainty, that may potentially exacerbate or worsen the appearance of the rash[4-6].

A comparison between drug evoked rash and tinea corporis rash is listed in table 1.

One of the important differential diagnoses of a rash is the possible side effects of medications. Recognising medication side effect is critical as management consists of making as accurate a diagnosis as possible and instituting efficient and effective avoidance measure, except in those situations where the suspect medication is essential and offers the best treatment for the patient's condition.

In selected situations, repeated exposure may be the best option to determine sensitivity but should only be considered with expert advice and informed consent[11]. It may require protection against and with potential intervention in the event that anaphylaxis develops, such as adrenaline auto-injector.

Antibiotic and Antiepileptic medications are of the most common medications to cause drug eruption and the cross-sensitivity rates between certain antiepileptic medications are considered high, especially when involving carbamazepine and phenytoin[12].

Between 1–10% of patients on carbamazepine develop a cutaneous reaction; over 85% of these are mild maculopapular reactions. Stevens-Johnson Syndrome and toxic epidermal necrolysis (SJS/TEN) incidence is estimated to occur in less than 0.06% of adults started on carbamazepine, whilst 0.04% or fewer develop drug reaction with eosinophilia and systemic symptoms (DRESS)[13].

The genetic alleles which are potential risk factors for SJS/TEN when using carbamazepine are HLA-B*1502 in the Southeast Asian population particularly those of Han Chinese descent, HLA-A*3101 in Caucasian patients and HLA-B*1511 in Japan, Korea and central China[14, 15]. People of Han Chinese descent should be screened for the presence of HLA-B*1502 prior to initiating carbamazepine therapy especially if being included in clinical trials[15].

It is crucial to consider cross sensitivity between anti-epileptic medications. Patients known to have serious skin reactions to carmazepine need caution when substituting to oxcarbazepine despite the advice to the contrary that claims only 10% cross-sensivity[16].

Phenytoin side effects include hirsutism, gum hypertrophy, maculopapular eruptions, generalized exfoliative dermatitis, SJS, TEN, erythema multiforme, vasculitis, follicular or pustular eruptions, fixed drug eruptions (FDE), angioedema, hypersensitivity reactions, purple hand syndrome, cutaneous necrosis, pigmentation changes, porphyria and linear IgA bullous disease[13].

Rash is also a common side effect of lamotrigine treatment, occurring in 8.3% of patients, with half of these withdrawing medications as a consequence[14]. It has been shown that slow introduction of lamotrigine may overcome the risk of a rash[17]. A head- to –head trial comparing lamotrigine with carmazepine showed that carbamazepine has greater propensity to develop a rash than does LTG[18]. HLA-A*2402 was recently confirmed

as a shared risk factor for SJS/TEN after exposure to aromatic antiepileptic medications, including lamotrigine[14]. Several studies have indicated that lamotrigine-induced rashes are more frequent in children than in adults, at least in the case of potentially life-threatening reactions[19, 20]. A study showed that females were at a higher risk of developing lamotrigine-induced rash than were males[21]. The risk of skin reaction is increased when the starting dose of lamotrigine is high, the dose is increased rapidly and when there is a combination with valproate. Valproate side effects also include non-scarring hair loss, petechiae, pruritus, and hypersensitivity syndrome[22, 23].

Conclusion:

The case of GM arose because the team that was treating him was especially concerned about AEM evoked rashes, although the appearance of the rash favored fungal infection. Because of the basis of the consultation, it was felt to be worth evaluating those factors to be considered when contemplating AEM evoked rashes, together with rashes evoked from other medications.

It was considered important to develop a logical approach to the general evaluation of rashes. This should reflect a step wise approach that is crucial to undertake when dealing with any medical condition, and should apply to evaluating rashes. As was the case with GM, rash pattern recognition is an important component of determining the cause of a rash, followed by selective testing and appropriate treatment. This requires clinicians to expand their appreciation of rashes and their appearance (pattern recognition) and to adapt a systematic approach when evaluating a rash.

Consent Declaration

Informed consent was obtained from the patient and next-of-kin for publication of this case report.

Conflict of interest

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Authors' contribution:

RB and SA conceptualised the manuscript. SA drafted the manuscript. RB supervised SA in writing the manuscript. All authors approved the final manuscript.

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