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Single Case

Serum Sickness after Equine Rabies Immunoglobulin in Identical Male Twins: Two Case Reports

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Keywords
Serum sickness · Equine rabies immunoglobulin · Twins

Abstract
We, hereby, report two cases of serum sickness in adult male identical twins who had received equine rabies immunoglobulin as a postexposure rabies treatment after cat scratches. The younger brother developed low-grade fever, polyarthritis, and multiple erythematous maculopapular eruptions, whereas low-grade fever and urticaria-like eruptions were detected in the elder brother. Both patients received a 7-day course of low-dose prednisolone and achieved good responses without recurrent attacks.

Introduction

Serum sickness is a rare reaction with clinical manifestations including fever, skin rashes, and arthralgia or arthritis. It was first described by a well-known Austrian pediatric clinician, von Pirquet [1], in 1905. He observed symptoms – including fever, rash, and joint pains – together with a delay in the formation of circulating antibodies following equine diphtheria antitoxin injections. Antigen-antibody interaction, so-called toxic bodies, was proposed as the pathogenesis for this phenomenon. This cascading immune reaction is subsequently categorized as type III hypersensitivity. The diagnosis is based on an exposure history of the

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causative agent, mainly composed of heterologous proteins, together with compatible symptoms and signs occurring 1–2 weeks after the first exposure [2].

Case Report

Case 1

A 19-year-old Thai man, the younger twin brother, came to the hospital presenting with pruritic rashes on all extremities and upper chest for 1 day. He had been in excellent health until 1 day earlier, when low-grade fever, joint pain, and rashes developed. Ten days earlier, he visited an emergency department after he had been scratched by a cat on the dorsum of his right hand. According to an avulsion wound classified as category III in contexts of a contact with a suspected rabid animal, anti-rabies vaccine (SPEEDA®, Liaoning Cheng Da Biotechnology, China) as a post-exposure strategy was initiated and oral amoxicillin/clavulanic acid was also prescribed for 3 days in terms of infection prophylaxis. After the skin sensitivity test on his right volar arm was negative, equine rabies immunoglobulin (TRCS ERIG®, Queen Saovabha Memorial Institute, Thailand) was then administered around the wound site, and the remainder was administered intramuscularly into the left gluteal region. Nine days later, he first noted an itchy rash on his right volar arm at the previous site where the intradermal equine rabies immunoglobulin (ERIG) skin test had been performed; by the following day, the rash became diffuse, involving the upper chest and all extremities together with low-grade fever as well as painful and swollen joints – including bilateral proximal interphalangeal and tarsometatarsal joints.

On examination, his temperature was 37.5°C, pulse rate 90 beats per minute, blood pressure 128/79 mm Hg, and the respiratory rate 18 breaths per minute. Skin examination showed erythematous partially blanchable papules coalescing into plaques on the volar area of his right arm (Fig. 1a), both lower extremities (Fig. 2b), and upper chest (Fig. 1c). Bilateral proximal interphalangeal and tarsometatarsal joints were swollen and tender along joint lines, particularly with passive movement. The remainder of the general examination was normal. Laboratory tests revealed that complete blood count, CH50, C3, C4, blood urea nitrogen, creatinine, and urinalysis were all within normal limits.

A diagnosis of serum sickness was made and treatment with oral prednisolone (20 mg/day) and cetirizine (10 mg/day) was initiated for 7 days. Two days after treatment, his fever and polyarthritis dramatically resolved and skin lesions on the upper extremities and upper chest disappeared with remaining bilateral multiple nonblanchable violaceous-to-erythematous plaques on both shins. With further medication compliance, the skin lesions disappeared without ulcers or scars at the 10-day follow-up visit. There were neither recurrent skin lesions nor other systemic involvements during the 2-week follow-up period as shown in Figure 2.

Case 2

A 19-year-old Thai man, the elder twin brother, came to the dermatology outpatient clinic with rashes on his right knee, both upper extremities, and both feet for 1 day. He had been in previous good health until 1 day earlier when he developed high-grade fever and skin rashes. Eight days earlier, he visited an emergency department due to cat scratches on his right knee. According to an abrasion wound with contact bleeding, anti-rabies vaccine (VERORAB®, Sanofi Pasteur, France) was injected at his left deltoid. After the skin sensitivity test on his right volar arm showed negative results, equine rabies immunoglobulin (TRCS ERIG®, Queen

Saovabha Memorial Institute, Thailand) was infiltrated around the wound and intramuscularly into the left gluteal region. A 3-day course of oral clindamycin was also given for infection prophylaxis due to his previous history of penicillin allergy. Seven days later, a brownish itchy rash first appeared on the right knee where ERIG was infiltrated; by the following day, pruritic urticarial rashes were also observed on both dorsal hands, elbows, and dorsal feet together with low-grade fever.

On examination, his body temperature was 38°C, pulse rate 60 beats per minute, blood pressure 138/85 mm Hg, and the respiratory rate was 18 breaths per minute. A solitary, large demarcated brownish painless patch above the right knee (Fig. 3a) and multiple urticaria-like eruptions on extensor surfaces of both arms (Fig. 3b), and dorsal areas of both hands and feet were noticed. The remainder of the general examination was normal. Laboratory results were unremarkable.

In this case, prednisolone (30 mg/day) and cetirizine (10 mg/day) were given orally for 7 days. His fever resolved and skin lesions became light brown on day 7 of oral medication administration as shown in Figure 4. Neither recurrent skin lesion nor other systemic involvement was detected at a follow-up visit on day 10.

Discussion

In developing countries including Thailand, where there remains a high incidence of dog bites – approximately 400,000 cases per year [3] – ERIG is the cornerstone component of rabies post-exposure treatment, particularly in unvaccinated patients, since it is roughly 6 times less expensive and thus more affordable compared with human rabies immunoglobulin. In Thailand, previous studies revealed that most adverse reactions from ERIG were acceptable and transient. The reported incidence of serum sickness varied from 0.87 to 6.19%, which seemed to depend mainly on purifying techniques and the amount of protein content [4, 5]. Moreover, females and individuals aged over 21 years had a significantly higher incidence of serum sickness to ERIG [6].

The term serum sickness is generally reserved for the syndrome caused by an immune reaction due to a heterologous protein-containing agent, which often contributes to cutaneous or systemic vasculitis, whereas serum sickness-like reactions were reported to occur after administration of various medications such as cephalosporins, penicillins, and rabies vaccine components [7–9]. As yet, the pathogenesis and the standard definition of as such drug reactions have not been well established. The diagnosis of these two reactions is mainly based on a history of causative agent exposure and compatible symptoms and signs occurring 1–2 weeks after the first exposure. The cutaneous findings – including urticarial, palpable purpura, papules, and maculopapular lesions – often begin at the region around the injection site before extending throughout the body, typically sparing the mucous membranes [1]. Other investigations, i.e., complement studies and histological findings, are not recommended as the routine assessment due to the lack of specificity; moreover, the latter profoundly depends on patterns of the clinical manifestations. Classically, it is expected to see decreased C3 and C4. However, we did not have their baseline results in order to compare the values. Furthermore, we assumed that blood samples were taken quite early. Lawley et al. [2] found that C3 and C4 decrease ranged from 29 to 100% and from 19 to 100% of baseline levels, respectively. C3 and C4 reached nadir values at day 10.6 ± 3 and 10.0 ± 3, respectively. Consistent with these findings, Ko and Chung [10] also reported a patient who suffered from serum sickness after having received antivenom with normal C3 and C4. It is also possible that, aside from the time

during which the blood samples were collected, the severity of conditions might play another important role.

Although the concomitant antibiotics and rabies vaccine both cases received could also be possible causes of serum sickness-like reactions, the primary cutaneous reaction – occurring on the skin sites previously injected with ERIG including the skin sensitivity test as well as the ERIG local infiltration around the wound to neutralize rabies virus – distinguishes itself from the others. After the intramuscular administration of a 5-dose rabies vaccination regimen, the recurrence of symptoms and signs of serum sickness-like reactions was not observed after subsequent rabies vaccination as scheduled in a later steroid-free period. Hence, it was again confirmed that ERIG was mostly suspected as the culprit causing serum sickness.

According to clinical manifestations including acute fever, rashes, and joint pain, other possible causes can be categorized into infectious etiologies and noninfectious etiologies. Infectious etiologies include viral exanthems (dengue infection and chikungunya virus), scrub typhus, acute rheumatic fever, and scarlet fever. Noninfectious etiologies include acute lupus erythematosus and cutaneous vasculitis. However, given the very characteristic presentation and clinical course in both patients, the most likely diagnosis is serum sickness. Therefore, due to the cost-effectiveness, we decided not to do extensive investigations but choose to closely follow up the disease progression.

We hereby reported the first two adult twins in Thailand who were simultaneously diagnosed with serum sickness after having received ERIG for the first time in their life – in spite of utilizing the ERIG brand with the low-protein content, i.e., 1 mg/mL [11]. To date, many conditions – including age, dose, and heterologous protein – were claimed as risk factors for serum sickness syndrome [12, 13]; nonetheless, being a twin sharing the same genotype has yet been postulated as a risk factor. This is, so far, the first report of serum sickness after having administered ERIG in twins. Hence, further prospective observations will be needed to investigate the association between the occurrence of serum sickness and previous reactions of individual monozygotic or dizygotic twins. Also, further studies are needed to elaborate on the exact mechanism. This might help us to decide whether or not, when treated with immunoglobulins, twins may need close monitoring of adverse reactions in order to provide better care. The best prevention of serum sickness is, so far, avoidance of antitoxins that might cause serum sickness; therefore, pre-exposure rabies vaccination is recommended especially where a high incidence of mammal bites is still reported [14]. We would suggest human rabies immunoglobulin for them, instead of ERIG, because of the lower incidence of serum sickness and other side effects [5, 6]. Owning to the skin sensitivity test results which were negative in our cases, our findings confirm previous studies which have reported that this conventional test had poor predictability of anaphylaxis or serum sickness reactions [15]. Thus, monitoring of acute and delayed adverse reactions is essential regardless of types of immunoglobulins.

Despite unavailable standard treatment of serum sickness, the use of glucocorticoids was recommended for cases with severe symptoms (i.e., high-grade fever, extensive vasculitis, and severe arthritis) based on case reports. These included prednisone (0.5–1 mg/kg per day) and intravenous methylprednisolone (1–2 mg/kg per day) with a total duration of therapy of less than 1 week [16, 17]. Another concerning point of view was a possible poor immune response after rabies vaccination in patients who received glucocorticoids particularly with a total of 20 mg/day or more of prednisone [18]. Nevertheless, this might have no significant influence on the efficacy of the vaccine in cases receiving short-duration glucocorticoid therapy – less than 2 weeks [19].

Conclusion

Two male identical twins were diagnosed with serum sickness of which typical systemic symptoms and signs developed approximately 2 weeks after administration of the non-human proteins, ERIG. The cutaneous manifestations included erythematous maculopapular rash and urticaria-like eruptions. Laboratory investigations – including complete blood count, complement studies, blood urea nitrogen, creatinine, and urinalysis – revealed no abnormalities. Due to the patients' moderate symptoms, we prescribed low-dose prednisolone for 1 week with good clinical response and no recurrence. Continuation of scheduled rabies vaccination was advised as ERIG was suspected as the culprit causing serum sickness.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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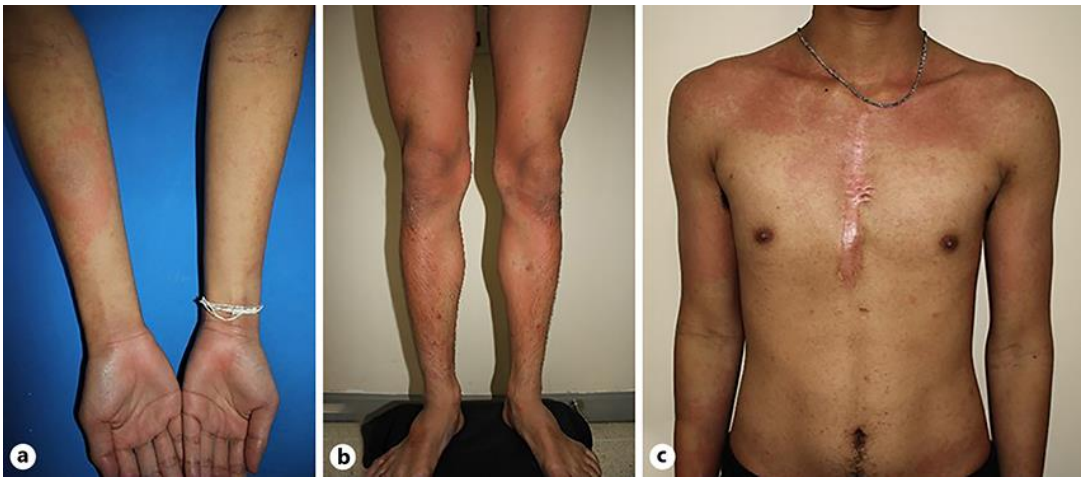

Fig. 1. Erythematous partially blanchable papules coalescing into plaques on the volar area of the right arm (**a**) where the intradermal equine rabies immunoglobulin skin sensitivity test was performed as well as on the lower extremities (**b**) and upper chest (**c**).

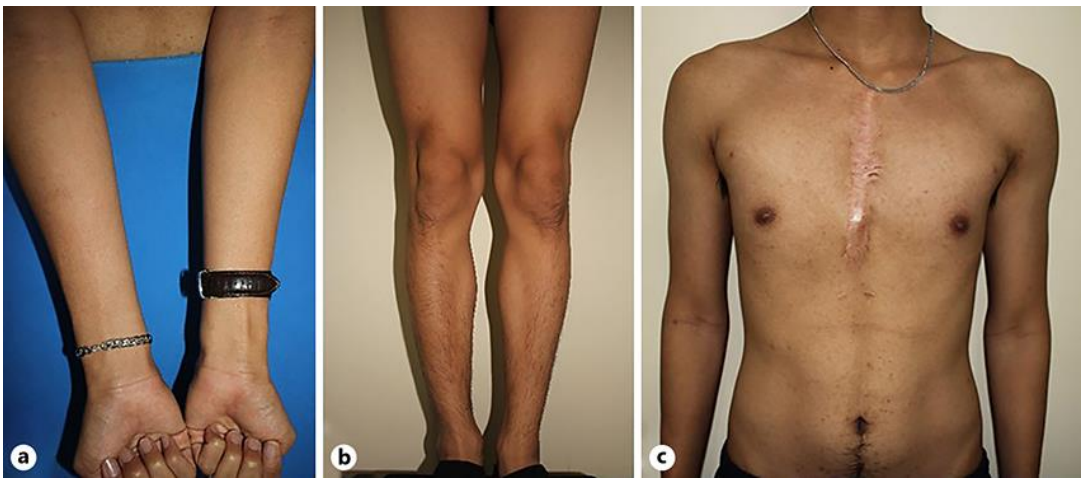

Fig. 2. Resolution of skin lesions on the volar right forearm (**a**), lower extremities (**b**) and upper chest (**c**) at a follow-up visit on day 10.

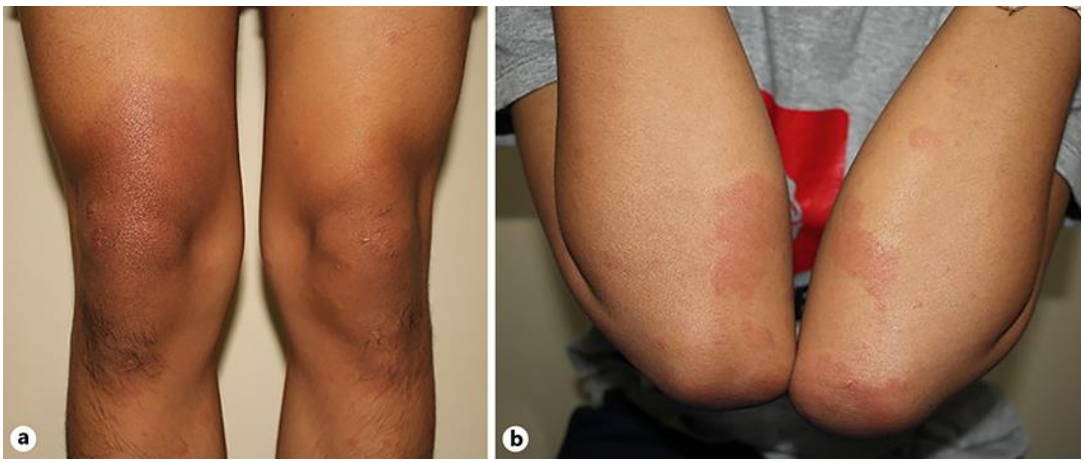

Fig. 3. A solitary, brownish, painless patch above the right knee (**a**) and multiple partially blanchable urticaria-like eruptions on extensor surfaces of both arms (**b**).

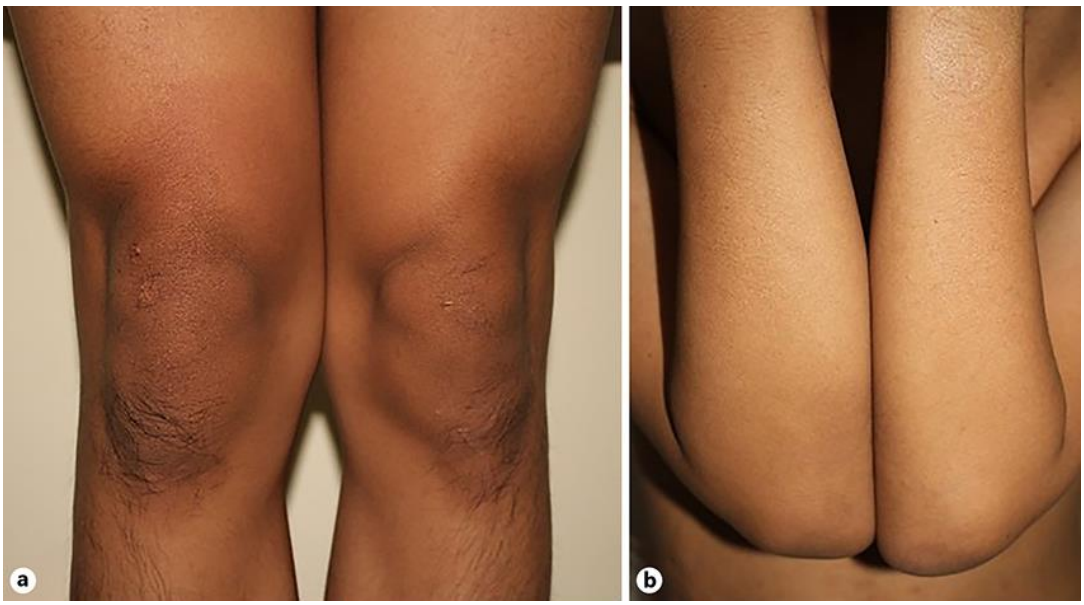

Fig. 4. Improvement of skin lesions on the right knee (**a**) and both arms (**b**) at a follow-up visit on day 7.