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Case report

Probable rivaroxaban-induced erythema multiforme in children: A case report

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ABSTRACT

Background: Limited data exists on the use of rivaroxaban for the treatment of pediatric patients. This report presents a case of probable rivaroxaban-induced Erythema Multiforme in Children. **Case Summary:** A female patient aged 5.5 years with antiphospholipid syndrome (APS) was administered oral rivaroxaban tablets 2.5 mg twice a day for 16 days. Subsequently, the patient developed a slight itching sensation on both feet and buttocks without an apparent cause. The following day, erythema multiforme appeared across the body in a scattered pattern. The erythema presented higher than the skin surface and partially merged into areas of the skin. Following an increase in the extent and degree of the erythema, all oral medications were ceased. Treatment with dexamethasone sodium phosphate injection, mometasone furoate cream, and mucopolysaccharide polysulfate cream resulted in an improvement of erythema multiforme. The erythema diminished and did not deteriorate subsequent to changing from rivaroxaban tablets to warfarin sodium tablets, and receiving nadroparin calcium injection.

1. Introduction

Compared with the traditional anticoagulant warfarin, the new oral anticoagulants (non-vitamin K antagonist oral anticoagulants, NOAC) have the advantages of rapid onset of action, less drug-drug interactions, no need for routine coagulation monitoring, and were recommended as the first-choice anticoagulant for deep vein thrombosis (DVT) by the American College of Chest Physicians (ACCP) (Kearon et al., 2016; Ruff et al., 2014; XARELTO®, 2017). Rivaroxaban, a NOAC of anticoagulant factor Xa, has been widely used in preventing and treating venous thrombotic diseases and stroke prevention in non-valvular atrial fibrillation. In December 2021, the U.S. Food and Drug Administration (FDA) approved rivaroxaban to treat pediatric patients. In March 2022, rivaroxaban was approved in China for treating and preventing the recurrence of venous thromboembolism in children. However, rivaroxaban is still off-label use in the treatment of APS, which is a rare acquired multisystem autoimmune thromboinflammatory condition. The primary common adverse drug reaction (ADR) of rivaroxaban is hemorrhage, with very few reports of ADRs caused by rivaroxaban, particularly among children. This case report details the experience of a paediatric patient with APS who developed erythema multiforme after treatment, which may have been caused by rivaroxaban. We provide thorough information on the patient's changes and outcomes to enhance awareness of the rare ADRs associated with rivaroxaban and ensure safe medication practices for children.

2. Case presentation

A female patient aged 5.5 years with APS was administered oral rivaroxaban tablets 2.5 mg twice a day for 16 days. The patient had weakness of the right limb without obvious cause, which gradually worsened. The abnormal signal of the left basal ganglia was shown on cranial MRI, and the possibility of cerebral infarction was considered.The patient was firstly admitted to the hospital for cerebral infarction (weakness of the right limb without obvious cause), and was given aspirin enteric-coated tablets 75 mg daily and multivitamin. After three days of aspirin, the patient stopped taking aspirin because of epistaxis, and the nasal mucosa was moistened with

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saline aerosol. Combined with relevant examinations and hematology consultation, it was considered that the patient complied with APS. Hydroxychloroquine sulfate tablets 0.1 g qd was orally administered to reduce the production of antiphospholipid antibodies. At the same time the epistaxis improved, low-dose aspirin enteric-coated tablets (50 mg daily) was added again. Three days later, rivaroxaban tablets 2.5 mg bid orally were added according to the consultation of the hematology department. The next day, the child had a mild reddish rash, and the doctor considered a viral infection. As the patient's general condition was good, and she was allowed to be discharged from the hospital. She continued to take rivaroxaban tablets, aspirin enteric-coated tablets, and hydroxychloroquine sulfate tablets for treatment.

A week after the first discharge, the child did not show any apparent motivation to experience mild pruritus in the feet and buttocks or any erythema, which the parents overlooked. The following day, a disseminated, red, polymorphic rash developed throughout the body, protruding above the skin level. The rash was accompanied by noticeable pruritus and occasional abdominal pain, primarily in the umbilical area, which lasted for approximately half an hour and resolved on its own. No joint pain or other concurrent symptoms were reported..The range and extent of the rash gradually increased, and all oral drugs were discontinued by the local doctor. Immediately, the patient went to the dermatology department of our hospital and was diagnosed with "erythema multiforme" (Fig. 1). Dexamethasone (0.5 mg/kg, 7.5 mg QD) was given intravenously for 3 days, and symptomatic treatment was given with topical ointment (mometasone furoate cream and polysulfone acid mucopolysaccharide cream).

Moreover, erythema has improved. For further treatment, the patient was hospitalized for a second time in the neurology department with no history of exposure to infectious diseases, no history of drug or food allergies, and no special family history.

3. Treatment process

Vital signs were monitored after admission. Dexamethasone sodium phosphate injection at a dosage of 8 mg per day from day 1 to day 6, cetirizine hydrochloride drops at a dosage of 2.5 mg twice daily from day 1 to day 14 were administered to manage inflammation and allergies. Mometasone furoate cream and Polysulfonic acid mucopolysaccharide cream applied from day 1 to day 14, were used to foster skin repair.Considering that the children need to continue treatment for APS, hydroxychloroquine sulfate tablets 0.1 g qd (day 3 to day 14) for oral anti-inflammatory therapy were restarted, and warfarin sodium tablets 1.5 mg qd (day 3 to day 7), nadroparin calcium injection 1500 iu q12h (day 3 to day 8) were given for anticoagulation at the same time., monitor the coagulation function after 1 week, keep the INR at 2–3, and adjust the medication plan according to the monitoring results. On day 6, the erythema slightly improved in the patient. Dexamethasone was reduced to 5 mg qd (day 7 to day 9). On day 8, the erythema improved, with occasional local transient itching, redness, and intermittent epistaxis (a small amount) without obvious incentive. On day 9, the INR was 1.92. Following the consultation with the hematology department, the patient continued to take the initial dose of warfarin orally, discontinued nadroparin, and re-examined the coagulation function on an elective basis. On day 10, according to the opinion of the dermatology department, the intravenous injection of dexamethasone sodium phosphate injection was changed to prednisone acetate tablets 30 mg qd (day 10 to day 14) orally. On day 14, the prothrombin time was 29.1 s, and the INR was 2.58. Considering that the patient was related to oral warfarin, there was no apparent new erythema or bleeding manifestations, and the treatment was not adjusted. On day 15, after a comprehensive evaluation, the patient was allowed to be discharged with medicines (prednisone acetate tablets,

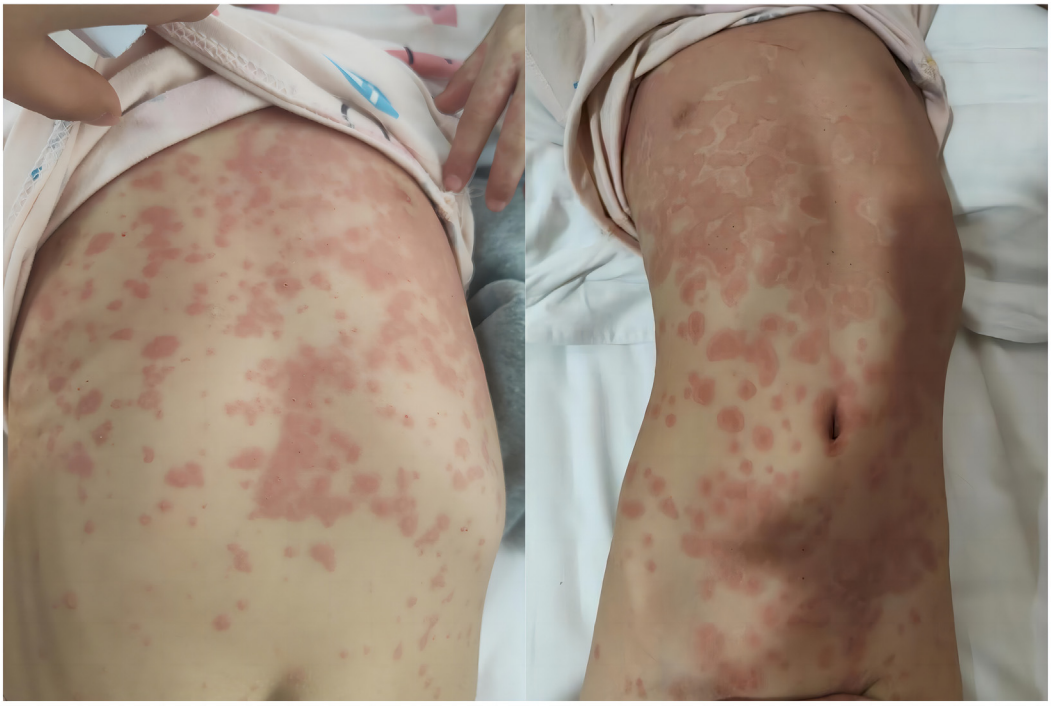

Fig. 1. Erythema Multiforme covering the whole trunk.

hydroxychloroquine sulfate tablets, warfarin sodium tablets) to continue the treatment, and instructed to monitor the blood coagulation function outside the hospital, pay attention to erythema changes, follow-up in thrombosis clinic of hematology department and the outpatient of dermatology department.

4. Analysis and discussion

4.1. Correlation analysis between rivaroxaban and ADR

The correlation was evaluated according to the Naranjo scale (Naranjo et al., 1981). Due to the antiphospholipid syndrome combined with rivaroxaban anticoagulant treatment, the pediatric patient developed a slight itching sensation on the feet and buttocks after 6 days without apparent causes, and scattered erythema multiforme occurred throughout the body the next day. The extent and degree of erythema were gradually aggravated, and rivaroxaban was stopped. After treatment, erythema multiforme was improved. The association between the use of rivaroxaban and the occurrence of erythema multiforme was evaluated as ‘‘probable” (Total Score:6).

In this case, 10 days before admission, there was no obvious incentive for slight itching in the feet and buttocks, and no apparent erythema was found in the child. The next day, scattered erythema multiforme occurred all over the body. The drugs used before the occurrence of erythema include aspirin enteric-coated tablets, hydroxychloroquine sulfate tablets, and rivaroxaban tablets. Among them, Aspirin was started 26 days before admission and stopped after 3 days of use; no rash occurred during this period. Nineteen days before admission, Aspirin was given again, and erythema multiforme occurred 10 days later. Hypersensitivity to a single NSAID usually occurs within 24 to 48 h of administration (Kowalski et al., 2013), and the allergic rash usually resolves immediately after Aspirin is discontinued (Lance et al., 2013), so the erythema multiforme may not be caused by Aspirin for this patient. However, the incubation period of different severe drug eruptions is quite different, and the clinical and pharmaceutical teams actively intervened in the patient’s condition to prevent further development. Therefore, Aspirin cannot be completely ruled out as the cause of erythema multiforme in this patient. Three days after admission, the patient was given hydroxychloroquine sulfate tablets again. After that, the rash was relieved, and no new erythema was seen. Therefore, the possibility of erythema multiforme caused by hydroxychloroquine sulfate tablets was ruled out. Literature reports (Rudd et al., 2018; Sasson et al., 2018; Vernon et al., 2016; Chaaya et al., 2016; Anis and Jandreau, 2021) show that systemic rash related ADRs caused by rivaroxaban mostly occur between 3 and 10 days after administration. The shortest time is after the first use, and the longest is 4 months. The patient started to use rivaroxaban tablets 16 days before admission, and erythema multiforme developed 7 days later; the time was consistent with the literature reports. Therefore, rivaroxaban may be the cause of erythema multiforme in this child.

4.2. Rivaroxaban and erythema multiforme of the skin

As a new oral anticoagulant, rivaroxaban plays a very important role in the treatment of children with deep vein thrombosis. At present, oral rivaroxaban has been found to be effective and well tolerated in long-term application (Gao and Jin, 2021; Diavati et al., 2022; Mills et al., 2023). Bleeding is the most common ADR, and erythema multiforme is rarely reported, and has no report in children.

Research has found that rivaroxaban has a low molecular weight. Short-term use is unlikely to prompt an immune response which could mimic an allergic reaction (Rudd et al., 2018). It has been reported that a 79-year-old female patient developed a systemic rash after taking rivaroxaban for a few days, and the pruritus and rash were completely relieved after 5–6 days of treatment with apixaban, suggesting a specific response to rivaroxaban (Sasson et al., 2018). The minor difference is that the binding of apixaban to free Xa is less dependent on the S1 and S4 binding domains due to their similar relative molecular masses, metabolic pathways, excipients, and affinity to free form Xa (Steinberg and Becker, 2014), so the specific mechanism of rivaroxaban causes the rash in patients is not known. After the ADR occurred in this child, the drug was discontinued and dexamethasone sodium phosphate injection, cetirizine hydrochloride drops were used for anti-inflammatory and anti-allergic treatment, and mometasone furoate cream and polysulfonic acid mucopolysaccharide cream were used to promote the skin Repaired, and re-administered hydroxychloroquine sulfate tablets for anti-inflammatory. At the same time, rivaroxaban was replaced by warfarin sodium tablets and nadroparin calcium injection for anticoagulation. After two weeks of treatment, the children’s erythema multiforme was relieved, APS was controlled, and smooth discharge.

5. Conclusion

This article discusses a case of suspected rivaroxaban-induced erythema multiforme in a pediatric patient, analyzes the relationship between medication and the ADR and the corresponding treatment, aiming to improve clinical understanding of rivaroxaban may cause erythema multiforme. Attention should be given to erythema multiforme caused by rivaroxaban during clinical practice.If skin abnormalities manifest, prompt discontinuation of the drug is recommended. Glucocorticoids and antihistamines may be utilized to treat symptoms, with medication adjustments required to maintain treatment of the primary disease. Furthermore, additional research into, the mechanism of erythema multiforme is necessary.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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