CASE REPORT
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Rare Case Report of Rash Associated with Risperidone Long-Acting Injection

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ABSTRACT

Skin rash is listed by the manufacturer as one of the adverse events that may be associated with risperidone long-acting injection (RLAI). An erythematous rash is described as an infrequent occurrence. The following is a case of a 26-year-old male who developed a diffuse erythematous and maculopapular skin rash on both arms after initiation of RLAI treatment. Previous exposure to oral risperidone was uneventful. Photographs of the rash are included. RLAI treatment was discontinued and diphenhydramine was prescribed. The rash responded to these interventions and was completely gone in 3 weeks. A re-challenge with oral risperidone produced no rash and was clinically effective. A literature review reveals few cases of RLAI treatment with rash and none including an uneventful oral risperidone re-challenge. A consideration of etiologies must include a reaction to an ingredient within the solute or delivery system and becomes an important clinical consideration in treatment planning.

FOCUS POINTS

- Risperidone long-acting injection (RLAI) is a common antipsychotic treatment used in clinical practice.
- Skin rash is an adverse effect with RLAI.
- Adverse effects may occur not only with chemical salts in medication but potentially with other ingredients in the solute and delivery system.
- Care should be taken when investigating adverse effects to medications.

INTRODUCTION

Risperidone is a benzisoxazole derivative and is available in oral and injectable forms. Risperdal long-acting injection (RLAI) is a combination of extended-release microspheres for injection and diluent for parenteral use. The extended-release microspheres formulation is a white to off-white, free-flowing powder. Risperidone is micro-encapsulated in 7525 polylactide-co-glycolide at a concentration of 381 mg risperidone per gram of microspheres. It is provided with a diluent for parenteral use, which is a clear, colorless solution. The diluent is composed of polysorbate 20, sodium carboxymethyl cellulose, disodium hydrogen phosphate dihydrate, citric acid anhydrous, sodium chloride, sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection.[1] RLAI has been shown in multiple studies to be useful in non-compliant schizophrenia spectrum disorders and is generally used on a biweekly basis.[2] The following is a case of a 26-year-old male who developed an erythematous, maculopapular skin rash on both his arms after he was started on RLAI.

CASE REPORT

Mr. A is a 26-year-old male who was seen at the authors' outpatient psychiatry clinic with a history of psychosis for 1 year. He reported hearing voices calling him "stupid" and he talked back to the voices. He was also observed to have paranoia, and thought that "people are up to something" and wanted to hurt him. His grandmother reported that he had trouble keeping up with his grooming and hygiene. The patient's previous psychiatric

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history included two hospitalizations in the previous year for paranoia and disorganized thoughts. His medications included trials of quetiapine and haloperidol at another clinic. He was reported to be noncompliant with the treatment.

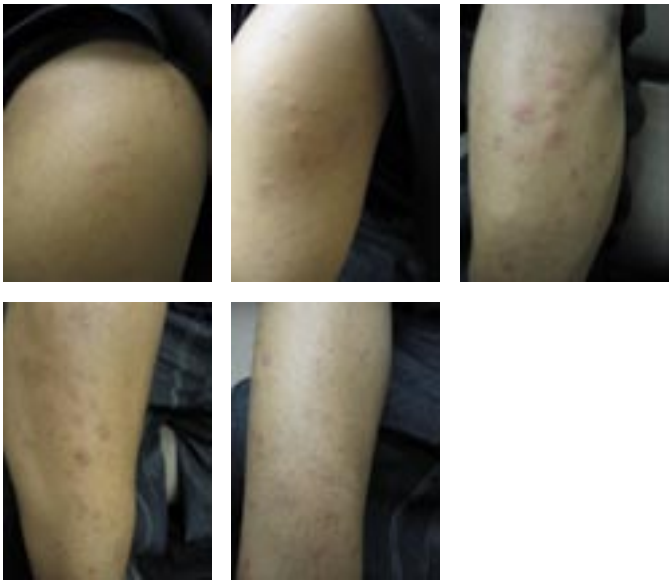
On mental status examination, Mr. A appeared his stated age, exhibited fair grooming and hygiene, and was guarded but cooperative. He did not display any abnormal movements or tremors. His gait and posture were normal. The patient spoke in a monotone voice and described his mood as "composed." His affect was significantly flat, though he did display inappropriate smiling. He denied the presence of any hallucinations during the interview but he had significant delay of his thought processes without the evidence of any delusional content. He was alert and oriented to time, place, and person. He had intact attention, concentration, remote, recent, and immediate recall. He had fair abstract thinking, insight, and judgment.

A general health assessment was conducted during the evaluation, and no active medical problems were noted. He was on no medical medications. He did not report any known food or drug allergies. The patient's body mass index and vital signs were found to be within normal limits. Lipid panel and electrolytes, including fasting blood sugar, were ordered and found to be within normal limits as well. A urine drug screen was also negative. A diagnosis of schizophrenia, chronic paranoid type, was made.

A detailed treatment plan was discussed with the patient and his family that included medications, individual supportive therapy, group therapy, and case management. Medication side effects and alternative treatment approaches were discussed. Mr. A agreed to the plan and was started on oral risperidone. The dose was gradually titrated to 3 mg BID. He responded well to this plan with a reduction in psychotic symptoms but within months he became inconsistent with appointments and taking his medication. His family was involved again and Mr. A agreed to be started on RLAI to ensure compliance. Side effects were again discussed. Mr. A was started on RLAI 25 mg injections, intramuscular, every 2 weeks. The dose was increased to 37.5 mg after 8 weeks (four injections) due to reduced but continued symptoms. He had a positive response to this treatment and his psychotic symptoms were extinguished. After the sixth dose of the injection, Mr. A began to develop generalized rash on both of his arms. Initially, the rash was mild and not reported to or seen by the physician. The rash gradually worsened over time as he continued treatment. It was identified at the time of the tenth injection. The rash had become erythematous, maculopapular, and diffuse. It had spread to bilateral hands, forearms, and arms. It was not localized to the site of injection. Photographs were taken at that time (Figure). The patient reported that he had denied these physical symptoms in previous appointments because the rash had not concerned him. He said after the rash developed, it had worsened after each injection. The patient had no other physical symptoms. Another discussion was held with the patient regarding medication side effects and a possible association of the rash with the intramuscular medication. The RLAI was discontinued and diphenhydramine 25 mg TID was begun. Mr. A was monitored regularly for rash and symptomatology. He was switched to haloperidol 2 mg BID and titrated to 5 mg BID.

After 2 weeks of regular observation, Mr. A's rash began to disappear. It completely resolved by the end of the third week. Diphenhydramine was then stopped.

FIGURE
MACULOPAPULAR SKIN RASHES



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FOLLOW UP AND RE-CHALLENGE ON ORAL RISPERIDONE

The patient's psychotic symptoms did not return with the haloperidol; however, he did develop medication side effects. These included psychomotor retardation, increased salivation, and further blunting of affect. These occurred within 8 weeks of medication use. He was reluctant to continue oral haloperidol.

Treatment options were again discussed with Mr. A and a decision was made to re-challenge with oral risperidone. Risks, benefits, and potential side effects were again

discussed. He was cross-titrated to oral risperidone with frequent monitoring for emergence of any rash and symptoms of psychosis. In 2 weeks, he was on oral risperidone 2 mg in the morning and 4 mg at bedtime. At this point, haloperidol was discontinued.

Mr. A reported continued resolution of the positive symptoms of schizophrenia and was also found to be more engaging and spontaneous. He did not report any side effects and none were noted. Vital signs remained normal, and laboratory results did not show significant change in lipid profile or Hba1c. There was widening of affect. He did not have psychomotor retardation or agitation. Motivation level improved. No rash was observed after 16 weeks of oral risperidone treatment. Mr. A became more regular with individual and group therapy appointments and has joined classes to get his general equivalency diploma.

DISCUSSION

Mr. A developed an erythematous, maculopapular rash while on RLAI. The rash was observed on both upper limbs and emerged within 12 weeks of initiating medication. The rash was diffuse and not localized to the injection site. It gradually disappeared after the medication was stopped and diphenhydramine was prescribed. It had completely resolved in 3 weeks. When re-challenged with oral preparation of risperidone, the patient tolerated the medication well. He did not have any rash after 16 weeks following the restart of the medication.

Antipsychotics are known to cause adverse cutaneous reactions in ~5% of the individuals for whom they are prescribed. The reported cutaneous adverse effects of antipsychotics include: exanthematous eruptions, skin pigmentation changes, photosensitivity, urticaria, and pruritus.[3-5] There have been reports of skin reactions with conventional antipsychotics.[6-9] Although the prevalence of skin reactions with atypical antipsychotics is reported to be lower than with typical antipsychotics,[10] newer reports linking skin reactions to olanzapine,[11-13] clozapine,[14-17] and other atypical antipsychotics are emerging. A recent case report[18] found risperidone oral solution to be responsible for facial flushing, rash, and skin desquamation in a patient with bipolar I disorder. Skin rash is listed in the manufacturer's brochure as one of the adverse events associated with long-acting risperidone injection. Erythematous skin rash, on the other hand, is listed as infrequent. One study[19] described an occurrence of injection site pain and non-specific skin reactions associated with RLAI. The authors' literature search also revealed a case of an allergic reaction to RLAI following oral risperidone use. No oral re-challenge occurred.[20]

CONCLUSION

In this case study, the etiology of the maculopapular rash is not definitive. It does, however, raise important clinical issues. The appearance of the rash, after initiation of RLAI treatment, suggests that further inquiry into a causal relationship between the two is warranted. The lack of rash during oral risperidone therapy suggests the role of the diluent or medication delivery system in the reaction. A re-challenge of RLAI would have provided useful information in this regard; however, clinical risk-benefit and safety concerns prevented this trial. Other explanations of the rash must also be considered. These include exposure to environmental irritants, shampoo, soap, or laundry detergent; over-the counter medication; or an undiagnosed medical condition. Additional investigation is required. Nonetheless, an awareness of this case within the clinical community should aid the physician in treatment planning and evaluation of skin rashes in patients receiving RLAI. This case also highlights the need for continued diligence in monitoring for adverse events while a patient is on medication. It underscores the phenomenon that patients may minimize, ignore, or deny symptoms they deem unimportant; direct questioning and observation are important tools to address this concern. ***PP***

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