

in the diagnosis of genetic disorders through the use of WES, numerous challenges and limitations to WES persist. There could be many possible mutations leading to a similar phenotype. The publication of variants discovered through targeted WES in association with extreme clinical phenotypes might allow for the identification of variant combinations likely to play a role in the phenotypic expression of the disease, if confirmed in similar cases.

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Severe delayed-type hypersensitivity to chloramphenicol with systemic reactivation during intradermal testing



Delayed-type hypersensitivity reactions to medication vary considerably in their presentation and include allergic contact dermatitis, maculopapular exanthema, fixed drug eruption, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome and toxic epidermal necrolysis.^{1,2} These delayed-type reactions generally commence from approximately 7 to 21 days after initial exposure to the drug, with subsequent reactions potentially occurring 24 to 48 hours after re-exposure.¹ Intradermal tests, patch tests, and oral challenge studies are commonly used in investigating delayed cutaneous hypersensitivity reactions.¹

This report describes a rare and novel case of severe delayed-type hypersensitivity to chloramphenicol (allergic contact dermatitis and maculopapular exanthema) with systemic reactivation during intradermal testing. To the best of my knowledge, this is the first report describing this particular reaction.

A 40-year-old male engineer underwent treatment for bilateral conjunctivitis with chloramphenicol 0.5% eye drops. After 48 hours he developed profound bilateral infiltrative erythema and edema involving his eyelids with erythematous papules periorbitally. Visual acuity was decreased. He also developed a generalized maculopapular exanthema at the same time as the periorbital dermatitis, which at skin biopsy examination was consistent with a delayed drug eruption (eosinophils, neutrophils, and perivascular inflammation noted). Chloramphenicol was immediately stopped. He was eventually admitted and treated with intravenous hydrocortisone and antibiotics to cover for possible periorbital cellulitis. He was apyrexial throughout, with a C-reactive protein level of 1.0 mg/L (normal level <5 mg/L). His periorbital dermatitis and maculopapular rash showed improvement during the next 4 days and he was discharged on steroid eye drops and made a good clinical recovery. He had no history of allergic disease but did recall being given chloramphenicol eye drops previously as a young adult.

Four months later, investigations were undertaken into a possible delayed-type hypersensitivity reaction to chloramphenicol.

Patch testing was contraindicated because of recent intense ultraviolet exposure and therefore he underwent skin prick and intradermal testing. Skin prick testing was performed with the undiluted stock solution of the intravenous preparation of chloramphenicol (100 mg/mL; Kemicetine; Pfizer, Tadworth, Surrey, United Kingdom). Histamine was used for the positive control and saline (0.9% NaCl) was used as the negative control. Skin prick testing read at 15 minutes was completely negative. Intradermal testing also was performed with the undiluted stock solution of the intravenous preparation of chloramphenicol in addition to serial dilutions (1, 10, and 100 mg/mL). Intradermal skin testing read at 15 minutes also was completely negative. On review 48 hours later, the intradermal testing sites corresponding to chloramphenicol at all dilutions (1, 10, and 100 mg/mL) were strongly positive with evidence of papules, vesicles, edema, induration, and erythema (Fig 1). He also developed significant bilateral eyelid edema, erythema, and ill-defined erythematous papules periorbitally with a mild generalized maculopapular exanthema, which had a strikingly similar appearance to his original drug eruption. Treatment consisted of oral steroids and antihistamines and he underwent a good clinical recovery during the next 5 days. No further investigations were performed and he was diagnosed with delayed-type hypersensitivity to chloramphenicol based on the clinical presentation, intradermal reaction, and skin biopsy findings. His prior exposure to chloramphenicol eye drops as a young adult was the presumed point of initial sensitization.

This report describes a novel case of severe delayed-type cell-mediated (type IV) hypersensitivity to chloramphenicol eye drops manifesting as allergic contact dermatitis and a maculopapular exanthema, with systemic reactivation during intradermal testing.

Chloramphenicol is a bacteriostatic broad-spectrum antibiotic widely used in the topical treatment of superficial bacterial infections such as conjunctivitis and otitis externa.³ Previously reported cases of delayed-type hypersensitivity to chloramphenicol have commonly described an allergic contact dermatitis, whereby the contact sensitization to chloramphenicol is typically elicited by application on mucous membranes (ie, eye drops and ear drops).⁴

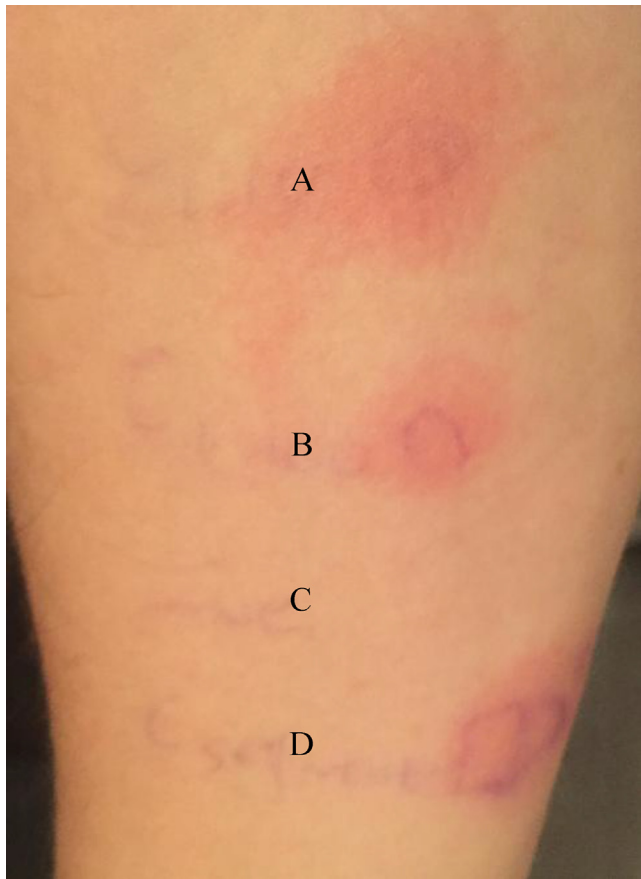


Figure 1. Delayed skin reactions during intradermal testing with chloramphenicol 10 mg/mL (A; 1:10), 1 mg/mL (B; 1:100), and 100 mg/mL (D; undiluted) and saline control (C). Results were positive with papules, vesicles, edema, induration, and erythema for chloramphenicol and negative for saline. Photograph was taken 48 hours after intradermal testing.

Conversely, more generalized delayed-type cutaneous reactions to topical chloramphenicol are rare, with only 2 prior cases reported in the literature (maculopapular rash and acute generalized exanthematous pustulosis).^{3,5,6} Chloramphenicol also has been shown to suppress lymphocyte transformation in previous in vitro studies.⁷ Diagnosing chloramphenicol allergy in the acute clinical setting can be challenging because of concurrent infection, with numerous cases often initially misdiagnosed and treated as severe periorbital cellulitis.⁵ In the present case, inflammatory markers were normal with absence of fever, which, although not a completely reliable indicator, can help differentiate between the causes.

Intradermal skin tests and patch testing are useful in diagnosing delayed-type hypersensitivity, with intradermal testing having reportedly higher sensitivity than drug patch testing.^{1,8} However, intradermal testing is contraindicated in very severe delayed hypersensitivity cutaneous reactions such as toxic epidermal

necrolysis and Stevens-Johnson syndrome because of concerns over potential systemic reactivation.⁸ Although patch testing has been commonly used for diagnosing chloramphenicol sensitization, there are very limited reports on the use of intradermal skin tests.^{4,6} In the present case, serial dilutions of chloramphenicol were used for the intradermal testing (undiluted, 1:10, and 1:100) to exclude any irritant reactions and thus ensure test validity.

Systemic reactions during skin testing in general are uncommon and are typically reported in the context of type I immediate hypersensitivity mediated by immunoglobulin E, with reaction rates ranging from 0.03% to 3.6%.^{9,10} In a prospective study by Bagg et al,⁹ the 12-month incidence of systemic reactions to intradermal testing was 3.2%. Systemic reactions were defined as any sign or symptom (excluding a local reaction) believed to be induced by the skin testing. These systemic reactions are often easily treated with oral steroids and typically undergo rapid clinical recovery.^{9,10} Systemic reactivation of delayed hypersensitivity reactions during intradermal testing is a very rare occurrence, which has little coverage in the literature and no reported incidence or reaction rates.

In conclusion, this rare case of delayed-type hypersensitivity to chloramphenicol with systemic reactivation during intradermal testing highlights that the physician should remain vigilant and be aware of the possibility of delayed systemic reactions during intradermal testing even if deemed low risk. Patients also should be counseled appropriately before testing. Furthermore, intradermal skin testing has been shown to be a useful alternative diagnostic tool for investigating delayed-type hypersensitivity to chloramphenicol.

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Sensitization patterns among patients with atopic dermatitis evaluated in a large tertiary care pediatric center

