THE PATIENT
24-year-old man

SIGNS & SYMPTOMS
– Prednisone therapy to treat nephrotic syndrome
– Diffuse maculopapular rash
– Pruritis

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THE CASE
A 24-year-old man with no past medical history was referred to a nephrologist for a 5-month history of leg swelling and weight gain. His only medication was furosemide 40 mg/d, prescribed by his primary care physician. His physical examination was unremarkable except for lower extremity and scrotal edema.

Laboratory values included a creatinine of 0.8 mg/dL (reference range, 0.6 to 1.2 mg/dL); hemoglobin concentration, 14.4 g/dL (reference range, 14 to 18 g/dL); albumin, 1.9 g/dL (reference range, 3.5 to 5.5 g/dL); and glucose, 80 mg/dL (reference range, 74 to 106 mg/dL). Electrolyte levels were normal. Urinalysis revealed 3+ blood and 4+ protein on dipstick, as well as the presence of granular and lipid casts on microscopic exam. A 24-hour urine collection contained 10.5 g of protein. Antinuclear antibody titers, complement levels, hepatitis serologies, and antineutrophil cytoplasmic antibody titers were all normal.

A renal biopsy revealed idiopathic focal segmental glomerulosclerosis. The patient was started on oral prednisone 40 mg twice daily.

Two days later, he developed a diffuse pruritic maculopapular rash. He stopped taking the prednisone, and the rash resolved over the next 3 to 5 days. He was then instructed to restart the prednisone for his nephrotic syndrome. When he developed a new but similar rash, the prednisone was discontinued. The rash again resolved.

THE DIAGNOSIS
Since the patient had already been taking furosemide for 6 weeks without an adverse reaction, it was presumed that the prednisone tablet was causing his rash. It would be unusual for prednisone itself to cause a drug eruption, so an additive or coloring agent in the tablet was thought to be responsible for the reaction.

We noted that the patient had been taking a 20-mg orange tablet of prednisone. So we opted to "tweak" the prescription and prescribe the same daily dose but in the form of 10-mg white tablets. The patient tolerated this new regimen without any adverse effects and completed a full 9 months of prednisone therapy without any recurrence of skin lesions. His glomerular disease went into remission.

DISCUSSION
Excipients are inert substances that are added to a food or drug to provide the desired consistency, appearance, or form. They are also used as a preservative for substance stabilization.

There are many reports in the literature of adverse reactions to excipients.[1-3] These include skin rashes induced by the coloring agent in the capsule shell of rifampicin[2] and a rash

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that developed from a coloring agent in oral iron.[3] Other reports have noted dyes in foods and even toothpaste as triggers.[4,5]

Hypersensitivity. Although a specific reaction to prednisone was considered unlikely in this case, type IV delayed hypersensitivity reactions to corticosteroids have been reported. The most common type of corticosteroid-related allergy is contact dermatitis associated with topical corticosteroid use.[6] Many cases of delayed maculopapular reactions are thought to be T-cell–mediated type IV reactions.[6]

Type I immediate hypersensitivity reactions to corticosteroids are also well documented. In a literature review of 120 immediate hypersensitivity reactions to corticosteroids, anaphylactic symptoms were more commonly reported than urticaria or angioedema.[7] Intravenous exposure was most frequently associated with reactions, followed by the intra-articular and oral routes of administration.[7]

Causative agents. The same literature review identified methylprednisolone as the most common steroid to cause a reaction; dexamethasone and prednisone were the least frequently associated with reactions.[7] Pharmacologically inactive ingredients were implicated in 28% of the corticosteroid hypersensitivity reactions.[7]

Additives suspected to be triggers include succinate and phosphate esters, carboxymethylcellulose, polyethylene glycol, and lactose. Interestingly, there have been reports of acute allergic reactions to methylprednisolone sodium succinate 40 mg/mL intravenous preparation in children with milk allergy, due to lactose contaminated with milk protein.[8,9]

Yellow dye was to blame. In our case, the 20-mg tablet that the patient had been taking contained the coloring agent FD&C yellow #6, an azo dye also known as sunset yellow or E-110 in Europe. Several reports have described adverse reactions to this coloring agent.[1,3] There were other additives in the 20-mg tablet, but a comparison revealed that the 10-mg tablet contained identical substances—but no dye. Thus, it was most likely that the coloring agent was the cause of the patient's probable type IV exanthematous drug reaction.

Our patient

The patient was instructed to avoid all medications and food containing FD&C yellow #6. No formal allergy testing or re-challenge was performed, since the patient did well under the care of his nephrologist.

THE TAKEAWAY

It's important to recognize that adverse drug reactions can occur from any medication—not only from the drug itself, but also from excipients contained within. This case reminds us that when a patient complains of an adverse effect to a medication, dyes and inactive ingredients need to be considered as possible inciting agents. JFP

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