When in Doubt, Blame the Drug

A 54-year-old woman with chronic renal disease was diagnosed with gout and prescribed allopurinol. Two days later, she was evaluated by her nephrologist, whom she informed about her new medication.

Subsequently, the patient developed fever and rash. Laboratory analysis indicated elevated transaminase levels and eosinophilia. She was admitted to the hospital.

During her stay, an infectious disease consultation was obtained, and the allopurinol was discontinued. When the patient's condition improved, she was discharged.

Following discharge, the patient resumed taking allopurinol, and her rash returned. Eleven days later, she returned to the hospital, where she was diagnosed with toxic epidermal necrolysis. She was found to have a desquamating rash covering 62% of her body. The patient was transferred to a burn center but eventually succumbed to multi-organ failure.

The patient's estate filed a medical malpractice lawsuit against the nephrologist alleging negligence—specifically, failure to diagnose toxic epidermal necrolysis and failure to review her medications more carefully.

OUTCOME

A $5.1 million verdict was returned against the nephrologist.

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COMMENT

Many medications cause rash and are subsequently withdrawn; in a few cases, the effects are life threatening. Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are relatively uncommon but potentially fatal examples.

From the limited facts presented, we know that a 54-year-old woman with established renal disease of unknown magnitude was prescribed allopurinol for gout and consulted the nephrologist two days later. It is unclear if the patient had the rash during the first visit with her nephrologist. But we do know that she was eventually admitted and maintained on allopurinol while she had the rash, pending infectious disease consultation. At some point, the allopurinol was apparently stopped and the rash improved. After discharge, the patient resumed taking allopurinol. The rash not only returned but also worsened, necessitating her readmission to a burn center.

TEN, like SJS, is often induced by certain medications, including sulfonamides, macrolides, penicillins, and quinolones. Allopurinol, phenobarbital, phenytoin, carbamazepine, valproic acid, and lamotrigine are frequently implicated as well.

TEN is rare but serious. The initial presentation may be subtle, with influenza-like symptoms such as malaise, fever, cough, rhinitis, headache, and arthralgia—and the most discriminating sign: rash.

The rash begins as a poorly defined, erythematous macular rash with purpuric centers. The lesions predominate on the torso and face, sparing the scalp. Mucosal membranes are involved in more than 90% of cases.[1] Pain at the site of the skin lesions is often the predominate symptom and is often out of proportion to physical findings. Over a period of hours to days, the rash coalesces to form flaccid blisters and sheetlike epidermal detachment.[2] In established cases, patients will nearly universally demonstrate Nikolsky's sign: Mild frictional contact with the skin results in epithelial desquamation and immediate blistering.

Management involves immediate withdrawal of the offending agent and hospitalization for aggressive management. The mortality rate is high (30% to 60%[3]) and generally attributed to sepsis or multi-organ failure.

As clinicians, we are sometimes hesitant to label a rash allergic—thereby forever disqualifying an entire class of useful agents from that patient. However, in this case, the fact that the rash occurred simultaneously with a constellation of signs and symptoms perhaps made the rash appear to be part of an infectious process and not a drug-induced reaction. That is the challenge with TEN and SJS: The symptoms are subtle, flu-like, and confounding.

Here, the nephrologist apparently did not take action to stop the allopurinol after the patient first developed the rash. The jury was persuaded that a reasonably prudent clinician would have recognized the clinical presentation and stopped the allopurinol—and

certainly not restarted it following discharge (especially after the allopurinol was stopped in the hospital and the rash began to improve).

This case brings to mind two physicians from my training who made an impression. The first was a second-year internal medicine resident. I remember quietly remarking to another student during rounds, "He is really good." Overhearing, an attending physician answered, "He is really good because in his workup he always considers a presentation as a function of an underlying process, and walks through each of those processes in formulating his differential."

"Walking through" various disease categories forces the clinician to consider them all: infectious, autoimmune, neoplastic, environmental/toxic, vascular, traumatic, metabolic, inflammatory. In challenging cases, I've found it helpful to step backward into those broad basic categories of disease and reconsider the clinical picture.

Here, doing so may have allowed the clinician to reconsider inflammatory and autoimmune processes and revisit the possibility of iatrogenic toxic/environmental causes (ie, the allopurinol). Perhaps the outcome of this case would have been different.

The second physician was a nephrology fellow, who left me with this piece of wisdom: "When in doubt, blame the drug." Since nephrologists are expert drug-blamers, I suspect the early stages of this unfortunate case presented a clinical challenge.

IN SUM

Before you "missile lock" onto a diagnosis, take a mental step back to consider broad categories of disease. **—DML** **CR**

REFERENCES

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