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On the Cover

What's the diagnosis? A 63-year-old woman with an aggressive B-cell lymphoma underwent therapy with high-dose methotrexate following bicarbonate-containing intravenous fluid prophylaxis. Acute kidney injury (AKI) developed over the next 48 hours with serum creatinine rising to 1.7 mg/dl. Urine microscopy revealed numerous brownish/gold methotrexate crystals both in clumps (cover image) and in casts. Acute kidney injury from methotrexate-associated crystalline nephropathy was considered likely. Intravenous fluids containing bicarbonate were continued with the goal of high urine flow rates ($>$ 150 ml/hour) and a urine pH of $>$ 7.0. Over the next 48-72 hours, kidney function improved with serum creatinine approaching baseline. Methotrexate is a dihydrofolate reductase inhibitor that is employed to treat various malignancies, in particular high-grade lymphomas. Methotrexate when employed in high doses has been described to cause kidney injury through multiple possible mechanisms. In general, intratubular crystal precipitation is the most commonly described form of acute nephrotoxicity. AKI may occur from some combination of tubular obstruction from the crystals or an inflammatory reaction to the crystals. The former cause may have been more likely in our patient due to the rapidity of AKI following methotrexate administration, but a component of interstitial inflammation is impossible to exclude without a kidney biopsy. Risk factors for intratubular precipitation of methotrexate and its metabolites include low urine pH, volume depletion with low urinary flow rates, and with high urinary methotrexate concentrations associated with high dose therapy. Another potential cause of AKI includes tubular apoptosis/necrosis from lipid peroxidation that is associated with decreased adenosine deaminase activity following methotrexate therapy. (*Images and text provided by Mark A. Perazella, MD, Yale University School of Medicine, New Haven, Connecticut*)