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On the Cover
What is the diagnosis? A 15-year-old with underlying Turner syndrome, hypothyroidism, and Guillain-Barre syndrome presented with symptoms concerning for meningitis and was treated with empiric antibiotics and intravenous acyclovir. Other medications included levothyroxine, ranitidine, furosemide and vitamin D. Kidney function remained stable; however, urinalysis revealed SG 1.020, pH 5.0, 1+ protein, 1+ glucose, and 3+ blood following acyclovir exposure. Urine sediment analysis demonstrated white blood cells, red blood cells, rare granular casts, and numerous needle shaped crystals (left panel), which were birefringent with polarization (right panel). These finding were consistent acyclovir-induced crystalluria. Acyclovir is one of a number of medications that is associated with crystal formation within the urine. Others drugs included on this list are sulfadiazine/sulfamethoxazole, indinavir, atazanavir, ciprofloxacin, methotrexate, ascorbic acid, ethylene glycol, triamterene, and amoxicillin. With these agents, either the drug or one of its metabolites may crystalize within the renal tubules. Crystal precipitation typically occurs due to one or more of the following factors: drug insolubility, high or low urine pH, sluggish urine flow rates, and underlying kidney disease. Acyclovir is unaffected by urine pH and crystal precipitation is generally driven by drug insolubility in urine when given in high, intravenous bolus doses to patients with underlying kidney disease or in the setting of volume depletion. Urinary pH plays a role for drugs such as ciprofloxacin, indinavir and atazanavir, which can precipitate in alkaline urine whereas sulfadiazine and methotrexate are insoluble in acid urine and more likely to precipitate at pH < 6.0. Clinically, patients may present clinically with asymptomatic crystalluria, crystalline-induced AKI, or sometimes nephrolithiasis. Prevention and therapy are directed at improving urinary flow rates, stopping or dose reducing the culprit drug, and when feasible, altering urine pH to enhance drug/metabolite solubility. Recovery of kidney function with drug removal is common; however, some patients develop CKD. (Images and text provided by José Antonio Tesser Poloni and Maria Solange Bressan Giordani, Irmandade da Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil and Mark A. Perazella, Yale University, New Haven, Connecticut)