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Suspected Kidney Disease: Putting Urinalysis Clues Into Context, Part 1

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ABSTRACT: Typical urinalysis results in patients with nephritic disease are proteinuria greater than 2 to 3 g/24 h, blood detected by dipstick and microscopic examination, and red blood cell (RBC) casts. Other findings may include cryoglobulinemia (both polyclonal and monoclonal), low complement levels, and gross hematuria. Characteristic urine findings in patients with nephrotic disease are proteinuria greater than 4 g/24 h, no blood or less than is seen in nephritic disease, and casts without RBCs. Nephrotic disease is also associated with edema, a low albumin level, and a high cholesterol level. An antineutrophilic cytoplasmic antibody (ANCA) assay is useful in determining the underlying cause of rapidly progressive glomerulonephritis. For example, in a patient with azotemia and cavitary lung disease, the presence of cytoplasmic ANCA suggests Wegener granulomatosis.

Urinalysis plays a key role in the diagnosis of renal disease. The results help distinguish between nephritic and nephrotic disease and can identify rapidly progressive glomerulonephritis and tubular necrosis.

In this 2-part series, we use a case-based approach to illustrate typical urinalysis results in common renal diseases. We show how these results can be integrated with findings from the history, physical examination, and other laboratory studies to arrive at a reliable diagnosis and to guide treatment.

Here, we focus on glomerular diseases. In a future issue, we will discuss acute renal failure, interstitial injury, and nephrolithiasis.

CASE 1: GLOMERULAR DISEASE

Presentation. Blisters and vesicles have appeared intermittently on the hands of a 32-year-old woman for about 6 months; the lesions seem to be related to sun exposure. After exposure, the blisters heal but leave areas of increased pigmentation.

She had previously used injection drugs but stopped 8 years ago. She is a moderate drinker; however, she has had several recent weekend binges. She takes no medications and has no contributory family history.

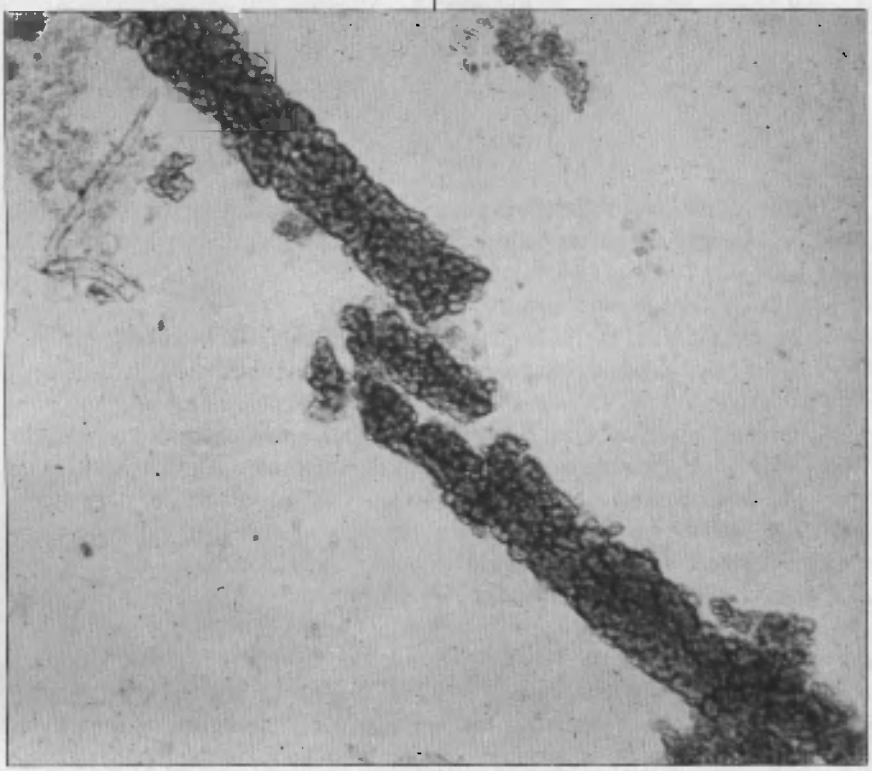
Physical examination. The patient looks her age and is in no apparent distress. Blood pressure is 142/98 mm Hg. She has vesicles and bullae on the dorsa of her hands that are consistent with porphyria cutanea tarda. Except for trace peripheral edema, the rest of the examination is normal.

Urinalysis results. Uroporphyrin levels are elevated. Microscopic examination reveals red blood cell (RBC) casts and RBCs (Figure 1). Dipstick data: protein, 2+; blood, 1+; specific gravity, 1.015; pH, 6.

Other laboratory findings. Aspartate aminotransferase level, 58 U/L; alanine aminotransferase level, 98 U/L; 24-hour urine protein measurement, 2.8 g; blood urea nitrogen (BUN) level, 9 mg/dL; creatinine level, 1.1 mg/dL. Serum albumin level is normal. Testing for hepatitis C virus antibody is posi-

tive; high titers of viral RNA are present. Complement levels are low, and cryoglobulinemia is present.

Discussion. Hepatitis C is a great mimic and has a number of extrahepatic manifestations (Table 1).[1-5] One of the most prominent is renal disease—specifically membranoproliferative or membranous glomerular disease, either with or without cryoglobulinemia. Porphyria cutanea tarda may also be a sign of underlying hepatitis C virus infection.



Photograph courtesy of Dr George Schreiner

Figure 1 – Red blood cell (RBC) casts and RBCs are visible in the urine of o womon with hepatitis C and membranoproliferative glomerulonephritis (Case 1) (×40). Dipstick data: protein, 2+; blood, 1+; specific gravity, 1.015; pH, 6. These findings are consistent with nephritic glomerulor disease.

Nephritic versus nephrotic disease. Urinalysis can be used to distinguish between nephritic (membranoproliferative) and nephrotic (membranous) states (Table 2). This distinction is ideal; in clinical practice there is significant overlap between the 2 categories—for example, patients with nephrotic disease in whom urinalysis reveals RBC casts and patients with nephritic disease who have massive proteinuria. However, the categories are still useful.

Typical urinalysis results in patients with nephritic disease—such as this woman—are proteinuria greater than 2 to 3 g/24 h, blood detected by dipstick and microscopic examination, and RBC casts. Other findings may include cryoglobulinemia (both polyclonal and monoclonal), low complement levels, and gross hematuria.

Characteristic urine findings in patients with nephrotic disease are proteinuria greater than 4 g/24 h, no blood or less than is seen in nephritic disease, and casts without RBCs. Nephrotic disease is also associated with edema, a low albumin level, and a high cholesterol level.

Table 1 – Extrahepatic manifestations of hepatitis C

Arthralgio	Porphyria cutanea tarda
Hypertension	Cryoglobulinemia
Purpura	Psoriosis
Vasculitis	Raynoud phenomenon
Lichen planus	Sicca syndrome
Presence of antinuclear antibodies	Presence of anti–smooth muscle antibodies
Low thyroxine level (presence of anti–thyroid peroxidase antibodies)	Monoclonal gammopathy
Membranous glomerulopathy	Diabetes mellitus
Membranoproliferative glomerulopathy	

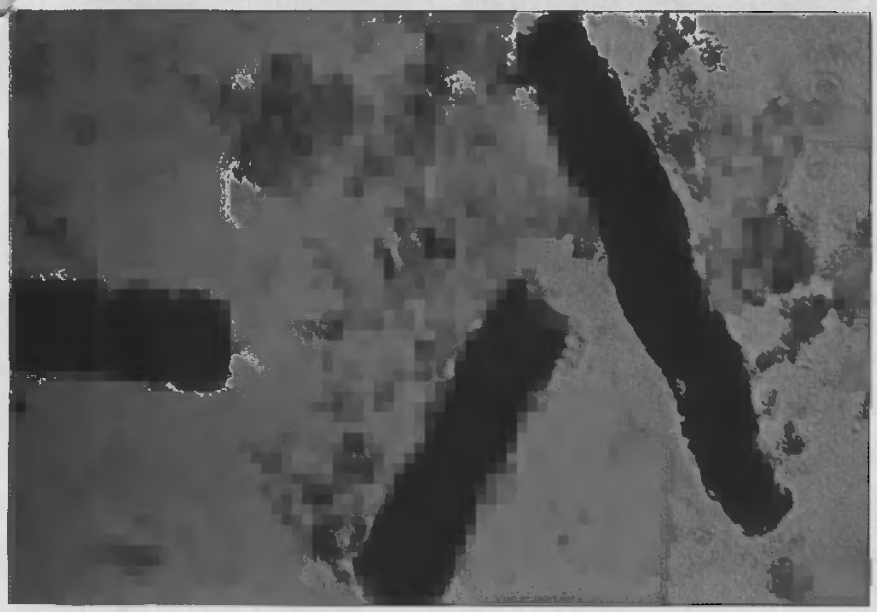
Data from Cacoub P et al. *Arthritis Rheum.* 1999[1]; Daghestani L, Pomeroy C. *Am J Med.* 1999[2]; Gumber SC, Chopia S. *Ann Intern Med.* 1995[3]; Andreone P et al. *Ann Intern Med.* 1998[4]; Mehta SH et al. *Ann Intern Med.* 2000.[5]

Table 2 – Characteristic findings in glomerular disease

Type of glomerular disease	Urinalysis results	Other findings*	Possible diagnoses
Nephrotic (membranous)	Protein, 4+; few RBCs; granular and hyaline casts (may show RBCs and RBC casts)	Hematuria less common than in nephritic disease; edema and hypercholesterolemia more common	Membranous glomerulopathy, nil disease, diabetes mellitus, amyloidosis
Nephritic (membrano-proliferative)	Protein, 2+ to 3+ (may show nephrotic-range proteinuria); many RBCs; RBC casts	Mixed cryoglobulinemia (polyclonal and monoclonal), complement levels may be low (eg, in MPGN), hematuria	MPGN, focal glomerulosclerosis (can have both nephritic and nephrotic features), PSGN

RBC, red blood cell; MPGN, membranoproliferative glomerulonephritis; PSGN, poststreptococcal glomerulonephritis.

*Tests that may be helpful include complement level measurement, serum and urine electrophoresis, antinuclear antibody, antistreptolysin-O, cryoglobulin measurement, hepatitis B and C antibodies, and renal biopsy (when indicated).



Photograph courtesy of Dr George Schrein

Figure 2 – Casts that appear to contain hemoglobin rather than red cells are seen in the urine of a man with oliguria and azotemia (Case 2) (×40). Dipstick data: protein, 2+; blood, 3+; specific gravity, 1.012; pH, 6.5. These findings are consistent with nephrotic glomerular disease. Idiopathic rapidly progressive glomerulonephritis was diagnosed.

In general, minimal change disease, membranous glomerulopathy, and amyloidosis are nephrotic diseases. Poststreptococcal glomerulonephritis, focal glomerulosclerosis, and membranoproliferative glomerulonephritis (MPGN) tend to be more nephritic than nephrotic. Hepatitis C may be associated with either MPGN or membranous glomerulopathy; cryoglobulinemia, low complement levels, and hematuria are less common in patients with hepatitis C virus infection and membranous glomerular disease.

Other diagnostic tests. In addition to urinalysis, certain noninvasive tests may aid diagnosis. Low complement levels are associated with MPGN, poststreptococcal glomerulonephritis, infectious glomerulonephritis (such as the glomerulonephritis that can accompany endocarditis or an infected ventriculo-atrial shunt), cryoglobulinemia, and lupus (which can be nephritic, nephrotic, or overlapping). Abnormal M protein levels suggest amyloidosis or a fibrillary glomerulopathy.[6] Glucose intolerance and urinalysis results typical of nephrotic disease

AN INNOVATIVE TELEVISION SPECIAL

CONTROLLING HSV2:

CUTTING EDGE MEDICAL REPORT

THE SILENT EPIDEMIC

HIV and AIDS are the hot topics of today's media when discussing sexually transmitted diseases. However, the incidence of genital herpes (HSV2) has dramatically increased by more than 30% since 1980 and people who contract it are more at risk of contracting HIV, so it's important to gain as much control over it as possible.

The virus may be spread even when there are no obvious signs of an outbreak, which is part of the reason that there are so many new cases. The worst aspect of genital herpes is the social stigma that accompanies it and the personal isolation some people suffer when they learn they have the virus. But because of research and clinical trials, there are new medications and better ways of controlling this virus than there were 20 years ago.

HSV2: The Silent Epidemic is co-hosted by Spotswood Spruance, M.D., Division of Infectious Diseases, University of Utah School of Medicine; Lawrence Corey, M.D., Head of Virology Division, Fred Hutchinson Cancer Research Center and Lawrence Stanberry, M.D., Ph.D., Professor, Department of Pediatrics and Director for the Center for Vaccine Development, University of Texas Medical Center.

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point to diabetes, the most common cause of glomerular disease.

Outcome of this case. Renal biopsy was performed to definitively diagnose the underlying disease; the results revealed MPGN. The patient responded to interferon and ribavirin therapy[7]; proteinuria decreased but did not disappear.

CASE 2: GLOMERULAR DISEASE AND ACUTE AZOTEMIA

Presentation. A 27-year-old man has had oliguria and fatigue for 6 weeks. He describes his urine in the morning as "Coke-colored." He denies rash, arthralgia/arthritis, pulmonary complaints, recent travel, and illicit drug use. He takes no medications. Family history and review of systems are otherwise negative.

Physical examination. Temperature is 37°C (98.6°F); heart rate, 98 beats per minute; respiration rate, 20 breaths per minute; and blood pres-

Table 3 – Causes of azotemic glomerular disease, classified by ANCA results

C-ANCA
Wegener granulomatosis
Polyarteritis nodosa (in some cases)
Overlap syndrome
Drugs
Malignancy
P-ANCA
Idiopathic
Polyarteritis nodosa
Microscopic angiitis
Churg-Strauss syndrome
Drugs
Malignancy

ANCA, antineutrophilic cytoplasmic antibodies; C-ANCA, cytoplasmic ANCA; P-ANCA, perinuclear ANCA.

Don't Let Patients

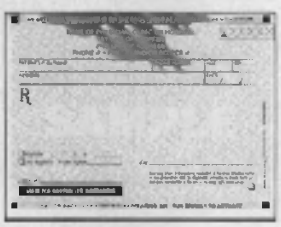
Purdue Pharma's 10-Point Plan to Without Compromising Patient

There have been many reports in the press recently about the abuse and diversion of prescription pain medications in certain isolated areas of the country.

We at Purdue Pharma have always been committed to proper pain management and to the safety and well-being of your patients and your practice. For this reason, we'd like to introduce you to our plan to help deal with this very important public health problem in the US. Dur 10-point plan includes the following initiatives:

1 CONTINUING MEDICAL EDUCATION PROGRAMS are being provided by Purdue in those regions of the US that have been most affected by prescription pain medication abuse. These high-quality, non-promotional educational programs teach healthcare professionals how to manage real pain and to reduce the diversion of prescription drugs by abusers.

2 TAMPER-RESISTANT PRESCRIPTION PADS are being offered by Purdue to physicians at no cost in regions with the highest reported incidence of prescription drug abuse.



3 DRUG ABUSE PREVENTION AND EDUCATION PROGRAMS FOR MIDDLE SCHOOL STUDENTS are being created by Purdue to diminish prescription drug abuse at the age when many kids start experimenting with drugs and alcohol. The company is working with the Community Anti-Drug Coalitions of America and other organizations to educate parents, teachers, and students about the social and emotional consequences of prescription drug abuse as well as its physical risks.

4 OPIOID DOCUMENTATION KITS are being offered to help physicians assess pain properly and to distinguish between legitimate patients with pain and addicts who fake symptoms.

5 ABUSE AND DIVERSION BROCHURES have been mailed to nearly 500,000 physicians and more than 60,000 pharmacists throughout the country, providing valuable information about prevention of prescription drug diversion.

Suffer in Silence

Prevent Prescription Drug Abuse Access to Proper Pain Control

6 A MAJOR STUOY OF PRESCRIPTION MONITORING PROGRAMS is being underwritten by Purdue. Working with the healthcare and law enforcement communities, the study will seek to develop a model prescription monitoring program that would prevent "doctor shopping" drug abusers and allow legitimate patients to receive appropriate prescription medicines.

7 EOUCATIONAL PROGRAMS WITH THE LAW ENFORCEMENT COMMUNITY, including the National Association of Drug Diversion Investigators (NADDI), several State Attorneys General and the National Association of State Controlled Substance Authorities (NASCSA), have been developed to better understand the undertreatment of pain and combat prescription drug abuse.

8 RESEARCH on the prevalence and root cause of the abuse of specific prescription drugs is being collected by Purdue-sponsored archers so that more effective prevention programs can be developed and evaluated.

9 CROSS-BOROER SMUGGLING is being addressed, in cooperation with the DEA, to prevent our products from being smuggled into the US from Mexico and Canada. Tablets sold in Canada and Mexico will have unique markings to enable law enforcement to identify where the product was dispensed.

10 ABUSE-RESISTANT MEOICINES are the #1 priority in our research labs. Purdue is spending tens of millions of dollars to test and to develop new forms of pain relievers that would be resistant to abuse while providing legitimate patients with safe and effective pain treatment.

Purdue is now – and always has been – committed to proper pain management and to the responsible use of opioids for legitimate needs. We are also committed to reducing prescription drug abuse, while at the same time ensuring that pain medications are readily available to the millions of patients in pain who need them.

The problem of pain in America can only be changed when the facts about it are acknowledged. Together, we can make a difference. Together, let's treat the pain.

PURDUE

Table 4 – Types of RPGN based on renal biopsy results

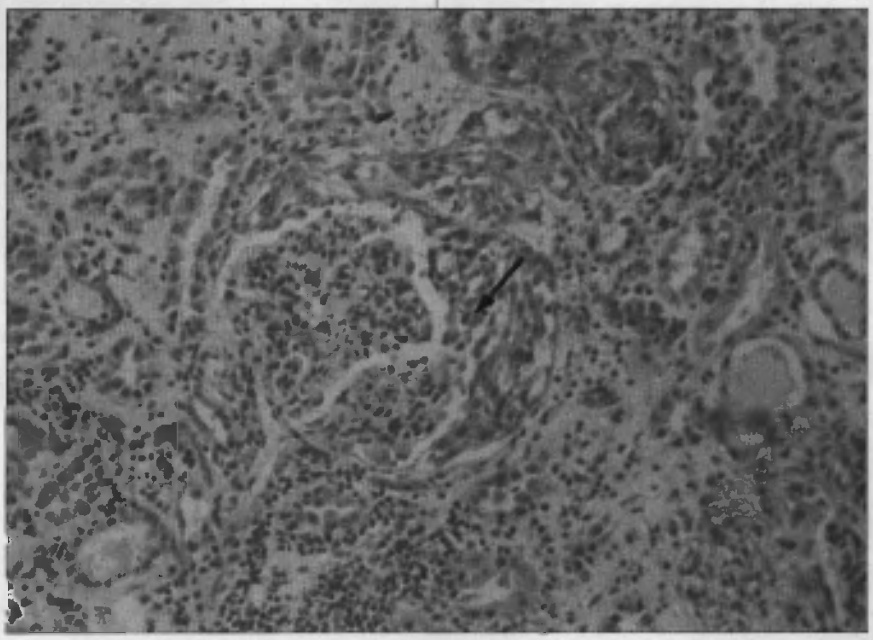
Type of RPGN	Renal biopsy findings	Examples
Disease that involves linear deposits along the glomerular basement membrane	Linear IgG on immunofluorescence staining	Goodpasture syndrome
Antigen-antibody deposition disease	Antigen-antibody complexes seen on electron microscopy or immunofluorescence staining	Systemic lupus erythematosus, Henoch-Schönlein purpura, poststreptococcal glomerulonephritis (a rare cause of RPGN)
Pauci-immune disease	No linear IgG or antigen-antibody complexes detected	C-ANCA–positive: Wegener granulomatosis (with pulmonary and sinus disease); P-ANCA–positive: Churg-Strauss syndrome, idiopathic RPGN

RPGN, rapidly progressive glomerulonephritis; C-ANCA, cytoplasmic antineutrophilic cytoplasmic antibodies; P-ANCA, perinuclear antineutrophilic cytoplasmic antibodies.

sure, 140/100 mm Hg. Results of skin, joint, neurologic, and cardiopulmonary examinations are all normal.

Laboratory and imaging results. BUN level is 37 mg/dL; serum creatinine level, 2.6 mg/dL. A complete blood cell count, metabolic panels, and chest radiograph are normal.

Given the setting of azotemia and oliguria, urinalysis results are reviewed (Figure 2). Microscopic examination shows casts that appear to contain he-



Photograph courtesy of Dr George Schreiner

Figure 3 – A crescent (arrow) is evident in this section of a glomerulus from a renal biopsy performed in a man with idiopathic rapidly progressive glomerulonephritis (RPGN) (Case 2) (hematoxylin-eosin, ×100). Crescents are inflammatory, cellular fibrin caps that are seen in the glomeruli of patients with RPGN.

moglobin rather than RBCs. Dipsti[c] data: protein, 2+; blood, 3+; specific gravity, 1.012; pH, 6.5.

Results of the noninvasive renal workup do not reveal a specific diagnosis. A renal ultrasound study is ordered; the results are consistent with acute renal parenchymal injury—normal kidney size, no obstruction, so-called medical renal disease. (Medical renal disease refers nonspecifically to injured kidneys that demonstrate a characteristic increase in echogenicity.)

Discussion. Urinalysis has an integral role in detecting the cause of glomerular disease in patients with acute or subacute renal failure that has resulted from rapidly progressive glomerulonephritis (RPGN)—also known as crescentic glomerulonephritis. Although urinalysis alone may not lead to a specific diagnosis in RPGN, it does provide an important starting point.

Acute or subacute renal fail[ure] can result from obstruction, rena[l] parenchymal injury (glomerular or interstitial), or acute tubular necrosis. Urinalysis results that show protein-

CLINICAL HIGHLIGHTS

❑ Although the nephrotic and nephritic categories are not absolute and may overlap clinically, they are still useful. In general, minimal change disease, membranous glomerulopathy, and amyloidosis are nephrotic diseases. Poststreptococcal glomerulonephritis, focal glomerulosclerosis, and membranoproliferative glomerulonephritis (MPGN) tend to be more nephritic than nephrotic.

❑ Low complement levels are associated with MPGN, poststreptococcal glomerulonephritis, infectious glomerulonephritis (such as the glomerulonephritis that can accompany endocarditis or an infected ventriculo-atrial shunt), cryoglobulinemia, and lupus (which can be nephritic, nephrotic, or overlapping). Abnormal M protein levels suggest amyloidosis or a fibrillary glomerulopathy.

❑ In a patient with rapidly progressive glomerulonephritis (RPGN), a livedo reticularis rash and a positive test for hepatitis B virus antigen suggest polyarteritis nodosa.

❑ RPGN can be classified into 3 types based on renal biopsy with electron microscopy examination and immunofluorescence staining: disease that involves linear deposits along the glomerular basement membrane, antigen-antibody deposition disease, and pauci-immune disease (in which there is no deposition of linear IgG or antigen antibodies).

uria and a glomerular rather than interstitial or acute tubular necrosis sediment point to glomerular injury as the cause of renal failure.

Physical examination and imaging results. In patients with azotemic glomerular disease, urinalysis results need to be interpreted in the context of a thorough physical examination and a chest film, because the underlying cause may affect multiple organs and/or systems. For example, Wegener granulomatosis involves the lungs and sinuses; polyarteritis nodosa, the blood vessels and skin; and Churg-Strauss syndrome, the lungs and neurologic system.[8]

Other diagnostic tests. Many tests that are used to categorize glomerular diseases in general (eg, complement measurement) are helpful in patients who have RPGN. The antineutrophilic cytoplasmic antibodies (ANCA) assay is particularly useful (Table 3).[8-10] ANCA positivity, together with classification as cytoplasmic ANCA (C-ANCA) or perinuclear ANCA (P-ANCA), significantly narrows the differential diagnosis.

When cavitary lung disease, azotemia, and C-ANCA are present, Wegener granulomatosis is the most likely diagnosis. A livedo reticularis rash and a positive hepatitis B virus antigen assay suggest polyarteritis nodosa. In a patient with mononeuritis multiplex, a positive P-ANCA assay is evidence of vasculitis; peripheral nerve infarcts and asthma in a patient with mononeuritis multiplex strongly suggest Churg-Strauss syndrome.

Role of biopsy. RPGN can also be classified into 3 types based on the results of renal biopsy with electron microscopy examination and immunofluorescence staining (Table 4).

Outcome of this case. This patient had a positive P-ANCA assay and biopsy results that were consistent with pauci-immune RPGN (Figure 3). In the absence of evidence of other diseases (eg, asthma, Churg-Strauss syndrome, polyarteritis nodosa) and of other contributory findings, idiopathic RPGN was diagnosed. The patient was given prednisone and cyclophosphamide, and the azotemia was arrested. ■

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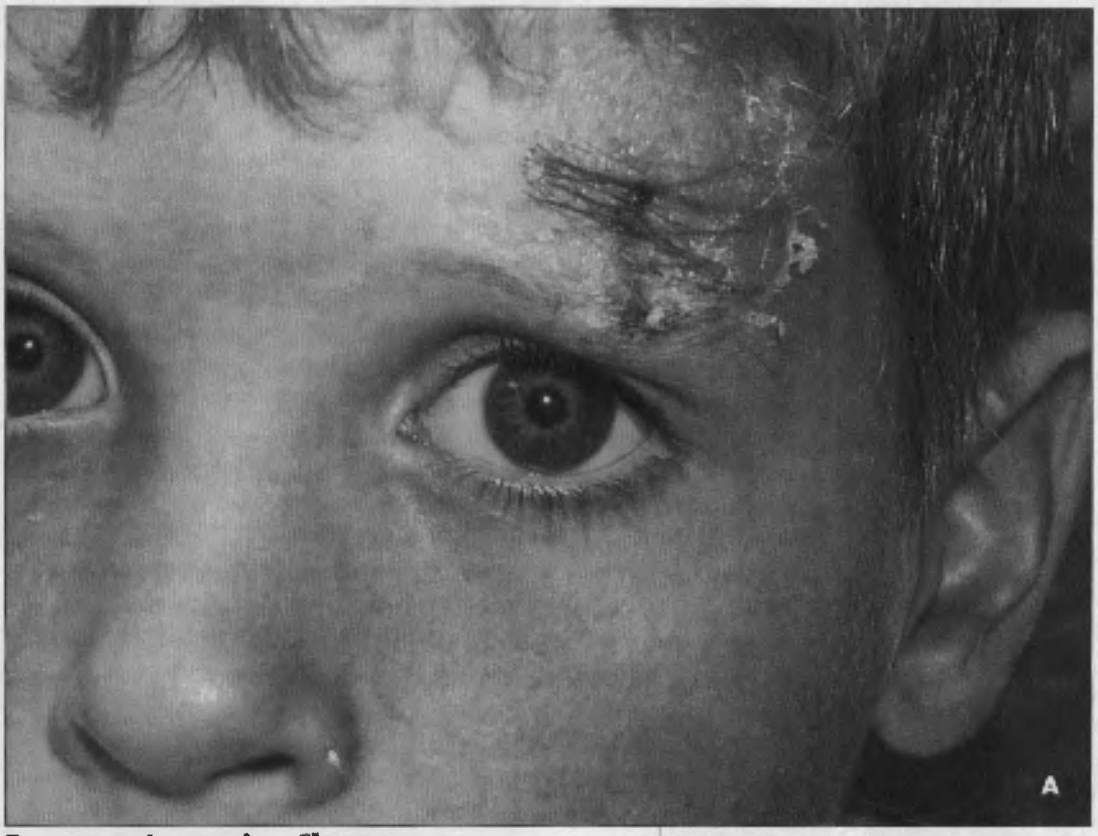
Foresee Your Next Patient

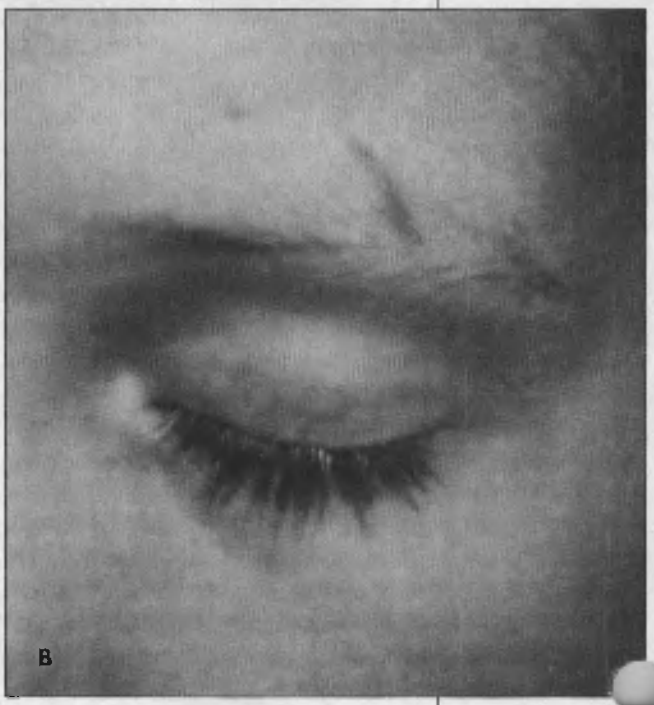


Emergent Laceration Closure

During a camping trip, a 7-year-old boy sustained a 1.5-cm laceration down to the bone above the left eyebrow. The laceration was clean and linear; it bled freely. The patient did not lose consciousness. The results of the neurologic and musculoskeletal examinations were normal.

Dr Jonathan S. Crane and John D. Schoonmaker, PA-C, of Wilmington, NC, who were at the campground, write that an inordinate amount of highway traffic resulting from a local bikers' rally prevented them from transporting the patient to a medical facility. Emergent wound closure had to be performed with available materials. After the wound was flushed, a household cyanoacrylate adhesive, Krazy Glue, was used to close the laceration. To add lateral support and to reduce the risk of wound dehiscence, Dr Crane embedded hair trimmed from the patient's scalp into a second layer of glue. To replicate wound closure tape, the hair was applied perpendicular to the laceration. Azithromycin suspension was available; 1 tsp (5 mL) was given initially followed by 2.5 mL daily for 4 days.

After 2 days, the wound and the glued hair were intact, and no infection or inflammation was present (A). Two weeks after the injury, the wound had healed well with a good cosmetic result (B). ■



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