Family Practice Grand Rounds

Hematuria in a Child

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DR. LAVERNE MILLER *(second year family practice resident):* This morning Dr. Grosh will present a patient who was admitted to the pediatric service through the Family Health Center.

DR. WILLIAM GROSH *(second year family practice resident):* Today's conference focuses on an 11-year-old Puerto Rican male who presented with hematuria and fever. He reported to the Emergency Room at night with a temperature of 103.4F; the hematuria had started some time that afternoon. This was the first time he had ever noted blood in his urine. He experienced no pain and described the urine as being light red in color. He had had a sore throat and an upper respiratory tract infection for 24 hours. The same day that he reported to the Emergency Room the school nurse had sent him home with a fever for which he later was given aspirin and an antihistamine (Contac). He had no history of sore throat, fever, or cold during the preceding month; however, his mother stated that he had developed an abscess in the left lower jaw for which he was to see a dentist the following week.

Past medical history revealed no previous hospitalizations or medications other than aspirin and Contac. He gave no history of asthma, diabetes, or hypertension; his only past illness was poison ivy. Immunizations were current, and he had no known allergies.

Family history was positive for diabetes and tuberculosis, and negative for kidney disease, hypertension, and arteriosclerotic vascular disease.

Social history: He is a sixth grader who likes school and has normal habits for his age.

Environmental history: He lives in a hot-air heated house.

Review of Systems: Essentially unremarkable. He denied any weight loss, vomiting, or diarrhea; he had had some cough, which was nonproductive. The rest of the systems were entirely negative.

Physical examination showed a well-developed, well-nourished, Puerto Rican male who was alert,

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cooperative, and in no distress. Height 60 inches, weight 92 pounds, temperature 102.4F, blood pressure 122/60 mm Hg, heart rate 100 beats per minute. Skin was hot and dry with good turgor. He had a lacy macular rash on his anterior chest. Examination of the head, eyes, ears, nose, and throat revealed that the nasal septum was mildly deviated to the right, the nasal mucosa looked somewhat raw, and the oropharynx was erythematous. There was no evidence of a dental abscess.

The neck was supple with no adenopathy. The lungs were clear. The heart showed a tachycardia of 100 to 110 beats per minute with a Grade 1/6 short systolic murmur heard best at the lower left sternal border and the apex. No S_3 or S_4 was appreciated.

The abdominal examination revealed hyperactive bowel sounds; there were no scars. Liver, kidney, and spleen were not palpable.

Genitalia: Uncircumcised; both testes descended; external meatus normal and foreskin retractable. Rectal examination showed good sph ncter tone with no masses.

Extremities: No growths, swelling, or tenderness. Full range of motion. Neurological examination was normal.

Chest and abdominal x-rays were within normal limits. Initial laboratory findings showed the following values: Complete blood count: white blood cells 9600/cu mm, segmented cells 74 percent, band cells 5 percent, lymphocytes 14 percent, monocytes 7 percent, red blood cells 5.1 million; hemoglobin 14.7 gm/100 ml; hematocrit 41.4 percent; platelets 288,400/cu mm. Partial thromboplastin time was 28 seconds, control 33.0 seconds. Electrolytes were within normal limits. Prothrombin time was 15.1 seconds with a control of 10.5 seconds. The urine at that time had a smoky reddish-brown color, specific gravity 1.025, 4+ albumin, with negative acetone, sugar, and bilirubin; dipstick showed a moderate amount of occult blood. Microscopic examination revealed 500 to 1,000 red blood cells per high power field; a small number of bacteria; a small amount of amorphous urates; and an occasional epithelial cell.

The following values were also noted: creatinine 0.9 mg/dl; antistreptolysin-0 (ASO) titer 250 Todd units; streptozyme titer 1:200. The SMA-12 was within normal limits. (Deviating from the published laboratory normal values were lactic dehydrogenase 233 international units, alkaline phosphatase 212 international units, and inorganic phosphorous 4.5 mg/dl. These values were not considered abnormal for a child of his age.) Sedimentation rate was 11 mm/hr. Blood cultures were negative. A 24-hour urine specimen showed 2200 mg protein/24 hr (normal value is 0 to 150 mg/24 hr). The value for urine sodium was 53 mEq/liter and for urine potassium, 49 mEq/liter. Creatinine clearance was 100 ml/minute. Urine cultures were negative. Throat culture showed only nonhemolytic alpha streptococcus (normal flora).

The following day his fever and hematuria persisted.

DR. JOHN SCHUBERT *(Chief, Division of Nephrology):* Essentially, we are confronted with an 11-year-old Puerto Rican male who had mild upper respiratory tract symptoms, red urine, a fever for 24 hours, questionable rash, a Grade 1 systolic ejection murmur at the left sternal border, and a normal CBC.

DR. GROSH: He did have a granulocytosis with a slight shift to the left.

DR. MICHAEL KITA *(second year family practice resident):* How much aspirin would a child this age have to ingest in order to increase the prothrombin time 50 percent?

DR. SCHUBERT: It does affect it, but I don't know how much is necessary. How about the ASO titer of 250?

RESIDENT: It ought to be repeated.

DR. SCHUBERT: It certainly is not impressive. How about the streptozyme titer of 1:200?

RESIDENT: Borderline.

DR. SCHUBERT: No, it's much more impressive than the ASO of 250. A 1:100 streptozyme titer is borderline abnormal. It doesn't tell how recent the strep infection is, but is indicative of a previous episode. To know what is happening, serial determinations are necessary. How about the alpha strep?

RESIDENT: Normal flora.

DR. SCHUBERT: Right. Not significant. How about the fever, heart murmur, and toothache?

RESIDENT: Blood cultures were negative.

DR. KITA: Subacute bacterial endocarditis (SBE) is a possibility.

DR. SCHUBERT: All right. That will be placed on the differential diagnosis list.

DR. SCHUBERT: What is the meaning of 2,200 mg of protein in the urine? (No audible response).

In the urine, 2,200 mg of protein suggests glomerular disease, provided it is not a very small protein such as Bence Jones protein. Except in Bence Jones proteinuria, anything over 2 gm almost always is due to glomerular disease. There are scattered suggestions in the literature that significant proteinuria can occur in tubular disease, particularly pyelonephritis, but it certainly is unusual. Once the proteinuria exceeds 2 gm/day, the same pathologic processes which cause nephrotic syndrome usually are involved. The only difference is that the liver can produce enough protein to compensate for a 2 gm loss each day, but usually cannot compensate for a 4 gm daily loss; therefore, with the greater loss, hypoalbuminemia and edema develop.

What about this urine sodium of 53 mEq/liter? Normal values on the laboratory slips read, "10 to 200 mEq/24 hours." Urine sodium of 53 mEq/liter and urine potassium of 49 mEq/liter in 24 hours in a child is not normal, high, or low. It is a relative value only, giving information based on the patient's sodium intake that day. Is the creatinine clearance of 100 ml/min normal?

RESIDENT: Probably a little low for an 11 year old.

DR. SCHUBERT: This report was not corrected for body surface area (BSA). Usually anything above 100 ml/min/1.73 M^2 BSA is normal. While 100 ml/min would be low-normal for adults, it is probably good in this child. If it had been corrected for body surface area, it would be about 12.. ml/min/1.73 M^2 BSA.

We said there is a possibility of SBE, and blood cultures were ordered. What else would you consider?

RESIDENT: Post-streptococcal glomerulonephritis.

ANOTHER RESIDENT: Wouldn't casts be present?

DR. SCHUBERT: Would the absence of casts rule out post-streptococcal glomerulonephritis?

SEVERAL VOICES: No.

DR. SCHUBERT: Why?

RESIDENT: They may be hard to find.

DR. SCHUBERT: They may be infrequent as casts are not present in every case of glomerulonephritis, at least not on every examination. However, in a carefully examined, concentrated sediment, they usually may be found. In a case like this, with so much albumin and so many red cells, casts may be expected to be present 99 percent of the time, upon careful examination.

RESIDENT: Is it ever difficult to distinguish between a red cell clot and a red cell cast?

DR. SCHUBERT: Yes, the laboratory has a problem with seeing clumps of cells and calling them casts. The laboratory is likely to report red cell or hemoglobin casts in only approximately one percent of the patients who actually have them. Also, hemoglobin casts usually are called granular casts by the laboratory; therefore, if the report indicates many granular casts in a patient with hematuria, be aware that some of them probably are hemoglobin casts.

A picture of a typical red cell cast is being circulated through the room. As you see, red cells simply cannot be identified. You will miss 95 percent of red cell casts if that is what you expect to see. Here are three more pictures showing the development of a red cell cast. First, you see red cells lying free in the tubule; next, you see a mass of deformed red cells in a tubule; finally, you will observe a coagulum in which individual cells no longer are identifiable. As the red blood cells pass through a tubule, they usually break down and end up in a gel of hemoglobin. Therefore, the common cast in glomerulonephritis is not really a "red cell cast" but a hemoglobin cast. The hemoglobin cast is one in which you no longer can identify individual red cells, but the classic rusty color of the hemoglobin remains with some vague shadows or lumhs which are shadows of the former cells.

From my examination the urine contained many red blood cell casts. In fact, there were no other casts. However, the red cell casts often are accompanied by granular casts. The red cells are trapped in a protein matrix as they float through the tubules.

Now we have red cell casts and proteinuria, so we say this patient has glomerular inflammation. When red cell casts definitely are present, with rare exception the diagnosis will be "glomerulitis." Two of these rare exceptions could be acute tubular necrosis or renal infarction. Any kind of glomerulitis will give you red cell casts. In a case involving oliguria and red cell casts, diagnosis probably is acute glomerulonephritis rather than acute tubular necrosis.

Alright, we have SBE and post-streptococcal glomerulonephritis. Is there anything else this patient might have? What's the differential in this

case?

RESIDENT: Is SBE an actual infection of the glomerulus?

DR. SCHUBERT: It's an immune process not caused by emboli or infection of the glomerulus per se, but secondary to active infection in some part of the vascular tree with the formation of immune complexes, which then are filtered and trapped in the glomeruli.

DR. KITA: If some of the symptoms are ignored, Henoch-Schönlein (H-S) purpura would have to be considered in the differential.

DR. SCHUBERT: Just what would you disregard?

DR. KITA: The 4+ albuminuria.

DR. SCHUBERT: That supports a diagnosis of glomerulitis and can occur in H-S purpura. What else would suggest H-S purpura, if anything?

DR. KITA: The history of upper respiratory tract infection, but elevated prothrombin time would be against it.

DR. SCHUBERT: What to do with the elevated prothrombin time is puzzling, but H-S purpura is definitely in the differential.

DR. KITA: He is in the right age group.

DR. SCHUBERT: Yes, and he did have a cold for some time. Often H-S purpura is precipitated by a viral infection.

DR. JOHN RANDALL *(Pediatrician and Chief, Division of Infectious Diseases):* It is going to be extremely difficult to distinguish between post-streptococcal glomerulonephritis and H-S purpura.

DR. SCHUBERT: Correct, it may take a biopsy. H-S purpura causes a segmental disease not as diffuse as post-strep glomerulonephritis.

DR. RANDALL: About 30 percent of the patients with H-S purpura have evidence of streptococcal infection.

DR. SCHUBERT: Any other consideration?

RESIDENT: Some kind of hereditary condition, such as hereditary nephritis.

DR. SCHUBERT: Okay, hereditary nephritis is in the differential. It must be considered, especially at this age when its initial expression is not uncommon.

DR. HERBERT TINDALL *(Associate Director of the Department of Family and Community Medicine):* How about poisons or toxins?

DR. SCHUBERT: Not as likely, as they are more apt to produce isolated proteinuria. The metals such as gold and mercury, and drugs such as trimethadione (Tridione) and paramethadione (Paradione) cause nephrotic syndrome, but red blood cell casts would be unusual.

There are three big categories of glomerulonephritis not listed here.

RESIDENT: Polycystic disease and neoplasms?

DR. SCHUBERT: They cause hematuria, but not red cell casts.

RESIDENT: Something like lupus?

DR. SCHUBERT: Lupus! And other collagen diseases. There are two categories left, both of which occur predominantly in children and teenagers, and together are as common as post strep.

RESIDENT: Membranous glomerulonephritis.

DR. SCHUBERT: Membranoproliferative glomerulonephritis. *Membranoproliferative!* Another name for that is chronic hypocomplementemic glomerulonephritis. Any other?

RESIDENT: Immune complex disease?

DR. SCHUBERT: Most forms of glomerulonephritis are immune complex diseases. Be more specific. All of these others are progressive disorders. What category does not progress and is more benign?

RESIDENT: Benign focal glomerulonephritis.

DR. SCHUBERT: Right! However, the amount of proteinuria makes this diagnosis more unlikely. Based on this patient's history of upper respiratory tract infection associated with hematuria, should any of these other diagnoses be excluded?

DR. MILLER: Perhaps post strep since it precedes glomerulonephritis by two or three weeks.

DR. SCHUBERT: There are some types of strep infection that precede the glomerulonephritis by two or three weeks. Be more specific. How long does a strep throat usually precede a glomerulonephritis?

DR. MILLER: About ten days.

DR. SCHUBERT: Yes, 10 to 12 days.

DR. RANDALL: Nephritis can probably occur at any time after the streptococcal infection, in contrast to rheumatic fever in which there is a definite delay period.

DR. SCHUBERT: Based on experimental animal studies, the time should be from 10 to 12 days. With strep throat, to have hematuria develop on the day of the fever's onset would be hard to explain.

DR. RANDALL: The normal time lapse between infection and hematuria is 10 to 20 days.

DR. SCHUBERT: If it occurred any sooner, it would have existed subclinically earlier.

DR. RANDALL: Once the streptococcal challenge exists, nephritis will not be prevented by administration of penicillin.

DR. SCHUBERT: To seriously and sensibly consider post strep in this case, one would have to say that this was a child with a preexisting nephritis who had an anamnestic response. An exacerbation can take place in two days. Children with any kind of upper respiratory tract infection who have an acute nephritis can experience exacerbations with acute viral or febrile illnesses, regardless of the basic glomerular pathology. The time sequence in this case is unusual for post-streptococcal glomerulonephritis, and the throat culture was negative. So the question is, could this patient have had a subclinical infection (in a patient who was not particularly health conscious) one to two weeks prior to the onset of recorded symptoms, from which he spontaneously recovered, and now present with sequelae? Should we make this assumption and treat him for a streptococcal infection?

RESIDENT: What is your diagnosis, post-streptococcal glomerulonephritis?

DR. SCHUBERT: No. Now there is no diagnosis. Which diagnosis do you want to pick? Or do you need more tests? Is a serum complement needed before deciding on a diagnosis?

RESIDENT: Yes. If it were greatly depressed, membranoproliferative glomerulonephritis would be a more likely diagnosis than post-streptococcal glomerulonephritis, since the former complement is normal the first day and takes a few days to drop.

DR. SCHUBERT: Alright, in which of these diseases would the complement be low?

RESIDENT: All of them.

DR. SCHUBERT: Not true, Theoretically, it is true, but practically in certain diseases it usually is low and in others it is higher. It is possible but unusual to find it low in Henoch-Schönlein purpura. Acute post-streptococcal glomerulonephritis usually has low complement, but it usually stays low not more than two weeks from the onset of symptoms. It is a classical model of serum sickness: one bolus of antigen complexed with complement drops the serum level, and with no antigen left, the complement returns to normal. Therefore, post-streptococcal glomerulonephritis is associated with a transiently low complement.

How about SBE, including any type of continuing source of blood stream infection, such as jugular shunts, arteriovenous shunts in the arms, etc? SBE usually has a low complement as long as the infection persists and is more commonly called "shunt nephritis" (since endocarditis is a less frequent cause).

Systemic lupus erythematosus (SLE) is associated with a low complement level when the disease is active. The complement usually returns to normal as the activity falls, but correlation is not perfect. In membranoproliferative glomerulonephritis (chronic hypocomplementemic glomerulonephritis), complement stays down regardless of treatment. There are exceptions. The other diagnoses on the differential list have normal complement levels, including benign focal, membranous, and hereditary glomerulonephritis, and Goodpasture's syndrome.

A complement study, therefore, would make possible the elimination of some of these diagnoses. A single C_3 complement was done. To enable any elimination, a total hemolytic complement must be done: C_3, C_2, C_4, all of which are components of complement. The reason is that C_3 is not always down. As a few patients have no lowered complement components, this test is not absolute, but it does aid in diagnosis.

RESIDENT: A hearing test may be valuable in eliminating Alport syndrome.

DR. SCHUBERT: Alport's form of hereditary nephritis has an increased incidence of hearing deficits which often are in the high frequency range and not clinical at this patient's age. Yes, this is a possibility. The problem in this case is that the child had a normal complement, a fever which persisted for five days, and negative cultures. On the fifth day of fever, since the streptozyme titer was positive and he did have an acute nephritis, it was decided, despite all the logic just presented, that the possibility that this was post strep had to be seriously reconsidered. In spite of the evidence against a post strep etiology, he was given penicillin at this point, and was afebrile the following day. That does not prove anything, but makes an immediate renal biopsy unnecessary.

There are two alternatives with such an acute, flagrant glomerulonephritis: do nothing, or act on

history and clinical findings and treat with penicillin. If this were acute post-streptococcal glomerulonephritis, the urine might have been negative in several weeks. If there were no improvement, renal biopsy would be indicated.

RESIDENT: Do you have any recent ASO titers?

DR. SCHUBERT: No.

RESIDENT: Was the fever due to persistent streptococcal infection and not to the glomerulitis itself?

DR. SCHUBERT: The question is, how do you treat a glomerulitis?

RESIDENT: Penicillin would not do anything for acute glomerulitis.

DR. SCHUBERT: The acute glomerulitis itself does not change, but can give the patient a fever.

If the patient has a bellyache, which is possible with acute glomerulonephritis, Henoch-Schönlein purpura must be considered. Because of abdominal pain and white blood cells in the urine, children with acute glomerulonephritis occasionally are operated on for acute appendicitis or treated for pyelonephritis. With glomerulonephritis, there might be equal numbers of red and white blood cells which can be misleading. The question remains: was this fever due to inflammation of his kidneys, to some other virus, or to a cause which ought to be treated with penicillin? The answer is not clear. A confusing factor was the patient's sedimentation rate of 11 mm/hr when his fever was 101F.

This child could have benign focal glomerulitis and an incidental cause of fever (sore throat), with the benign focal glomerulonephritis flared by the acute infection. Benign focal glomerulonephritis is very common. Children and young adults with it may have recurrent gross or microscopic hematuria that persists for years, usually without loss of renal function. Careful examination of a concentrated urine specimen usually will reveal red cell casts. With an acute infection, these patients get much sicker. Patients with benign focal glomerulonephritis usually do not have proteinuria, which excludes it as a diagnosis for today's patient.

In contrast, chronic hypocomplementemic nephritis is a rapidly progressive and difficult-to-treat disease in children. These patients usually have a persistently low complement with approximately five to ten percent having an intermittently normal complement. This is a possible diagnosis. If this child has persistent findings one month from now, particularly if his creatinine is elevated slightly, say to 1.2 mg/100 ml, or if he develops any degree of hypertension, then he will need to have a biopsy taken.

DR. KITA: Two questions: First, is it possible to feel confident about the diagnosis of benign focal glomerulonephritis without a renal biopsy?

DR. SCHUBERT: Confidence is warranted by observing red blood cell casts associated with varying degrees of hematuria, ranging from two or three red cells to gross hematuria, in an asymptomatic child or young adult with no azotemia, proteinuria, or hypertension. With mild proteinuria, confidence in this diagnosis must decrease.

DR. KITA: The other question is: regardless of the fact that this child has been on penicillin, would it not have been worthwhile to have obtained another ASO and streptozyme titer? If they had risen, the throat culture would have been proven inaccurate.

DR. SCHUBERT: Yes, it would have raised that possibility.

DR. RANDALL: The streptozyme titer was elevated significantly.

DR. SCHUBERT: The question is, was it changing, ie, is it higher than it was two weeks ago?

DR. RANDALL: Serial studies are not needed with streptozyme titer.

DR. SCHUBERT: Should this patient have been treated with penicillin initially?

DR. RANDALL: Yes.

DR. SCHUBERT: Before the cultures were back? This child had a fever of several days' duration. His heart sounds changed with his murmur increasing on the second day. He had a paradoxical split of the second heart sound, but after the second day it did not split again.

DR. RANDALL: Yes, it is wise in a case like this to treat with penicillin and then wait for the tests to come back and proceed from there. Strep is hard to document; therefore, it is necessary to go by the clinical history.

DR. MILLER: An elevated streptozyme titer and no history of penicillin for streptococcal disease in the past month would appear to be a good enough reason to treat it with penicillin at this time, regardless of the clinical findings.

DR. RANDALL: Elevated streptozyme titer warrants penicillin.

DR. SCHUBERT: With an elevated fever, early penicillin treatment may have hidden SBE, had that been the problem. This patient may develop other findings and require more cultures prior to treatment.

DR. JOHN SURRY: *(third year family practice resident):* There was a question of peridontal abscess or some other type of abscess in the mouth. Were anerobic cultures done?

DR. SCHUBERT: There were no clinical findings in the mouth.

RESIDENT: Does fever accompany benign focal glomerulonephritis?

DR. SCHUBERT: No.

RESIDENT: Should these young people be placed on bedrest?

DR. SCHUBERT: A child with a post-streptococcal glomerulonephritis with significant hypertension and grossly red urine should be placed on bedrest, up to several days if his/her condition is acute. Without gross hematuria, severe hypertension, or acute renal insufficiency, bedrest is not necessary. However, the child should not be allowed to engage in athletics until he/she has improved.

RESIDENT: How will this young man be followed?

DR. SCHUBERT: He will return in another month and be followed by Dr. Nystrom who will be asked to check his urine for abnormal findings. If his urine remains the same, another complement and creatinine should be done. If the creatinine has risen or the complement dropped, he will need a renal biopsy.

DR. MILLER: Thank you all very much. This has been a most informative and provocative conference on a subject which is frequently confusing and difficult to sort out.

Differential Diagnoses

1. Subacute bacterial endocarditis (including shunt nephritis)
2. Post-streptococcal glomerulonephritis
3. Henoch-Schönlein purpura
4. Hereditary nephritis (including Alport syndrome)
5. Systemic lupus erythematosus and other collagen diseases
6. Membranoproliferative (chronic hypocomplementemic) glomerulonephritis
7. Benign focal glomerulonephritis
8. Goodpasture syndrome