You're the Flight Surgeon

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You are the deployed squadron medical element flight surgeon at a small KC-135 Stratotanker forward-deployed location when a 46-yr-old boom operator presents with a few concerns. You fly with this aircrew member often both at home and on combat sorties together over Iraq and Afghanistan. He is an excellent in-flight air-refueling operator with no existing Flying Class III waivers and is in good health other than his recently elevated blood pressures, averaging 160s over high 90s. He is very nervous about his blood pressure because of his family history of heart disease. During the review of symptoms, he also admits to seeing a small amount of what appeared to be blood in his urine once or twice in the last year; these episodes presented without fever or dysuria. You ask the patient about recent illnesses and, in retrospect, he does remember having a nagging upper respiratory infection and sore throat that he thought may have been strep a few months earlier. He is also worried about continuing his flying duties and asks right away if this will ground him.

1. What should be your first step in beginning the medical investigation and ensuring aircrew flight safety?

A. Put the boom operator on duty not including flying (DNIF) and send him to the expeditionary hospital to be evaluated by an emergency medicine physician.
B. Caution the aircrew member to monitor blood pressures over the next 5 d with a calibrated cuff from your office. Begin laboratory studies.
C. Tell him not to worry about it and get back to tracking the index case of the viral gastroenteritis that has consumed a whole tent of marines at your forward operating base.
D. Conduct a complete history and physical; review social and historical risk factors.
E. B and D.

ANSWER/DISCUSSION

1. E. The prevalence of hypertension and prehypertension in military personnel has been shown to be unusually high;[14] multiple deployments and limited access to well-rounded dietary intake, in addition to the usual social and familial risk factors, contribute to this. Because of this high prevalence, routine treatment of flyers with monotherapy for essential hypertension has become commonplace. Nonetheless, each new case of hypertension must be worked up independently, especially in light of the possible presence of hematuria. A basic workup with laboratory studies combined with a good history and physical must be conducted to ensure all causes of secondary hypertension have been ruled out.

There are no significant findings of edema, cardiac murmurs, or abdominal bruits during the physical exam. The patient's average blood pressure after his 5-d check is 170s/100s; his paternal grandfather had his first heart attack before age 50, and most of his primary relatives have hypertension. He does not smoke or have a history of diabetes. His job before flying was in fuels from the age of 18 to 28, mostly involving JP-4.

Because of the relatively rapid onset of hypertension and possible history of frank hematuria, you obtain a resting electrocardiogram, chest x-ray, chemistry panel, thyroid studies, and urine studies. Unfortunately, some of the labs show abnormal results. The patient's serum creatinine was elevated and the urine dipstick was positive for 2+ protein and trace blood. Urine microscopy revealed red cell casts, dysmorphic red cells, and acanthocytes. There are, of course, limitations of the urine dipstick test for protein; in most cases, moderately increased albuminuria in the range of 30 to 300 $mg \cdot d^{-1}$ (formerly called microalbuminuria) cannot be detected with dipstick testing. A patient with severely increased albuminuria that is normally detectable by the dipstick (more than 300 $mg \cdot d^{-1}$, formerly called macroalbuminuria) may still have a negative dipstick if the urine is very dilute. Even if the urine dipstick is positive, the semiquantitative categories of albuminuria that are reported (trace, 1+, 2+, and 3+) are not necessarily reliable. In this case, due to the laboratory findings of microscopic hematuria and proteinuria, as well as the degree of combined systolic and diastolic blood pressures, it would be appropriate to DNIF the patient and consider a differential diagnosis. Because of the relatively poor sensitivity of urine microscopy for renal disease, you realize more definitive testing is necessary to confirm the diagnosis, including 24-h urine protein collection and more accurate studies of kidney function.[1,17]

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2. What might be a likely diagnosis, in the working differential at this point, taking into account the patient's family, social, and occupational history and otherwise benign physical exam?

A. Nephrolithiasis.
B. Primary (essential) hypertension.
C. Nephritic glomerular disease.
D. Collagen vascular disorder.
E. Nephrotic glomerular disease.

ANSWER/DISCUSSION

2. C. Although the other choices can all present with hematuria and proteinuria, nephritic glomerular disease is the most likely. Dysmorphic red cells in the urine, red cell casts, lipiduria, edema, and proteinuria are all harbingers of glomerular damage, but specifically acanthocytes, red cell casts, and lack of edema on exam point to a nephritic syndrome at this time. Acanthocyturia alone has been shown to be of assistance in ruling out glomerular causes of hematuria. Individuals without this finding in their urine have glomerular disease on confirmed biopsy only 2% of the time or a specificity of 98%.[8] Further testing for nephrotic changes, such as evaluation of urine protein over 3.5 $g \cdot d^{-1}$, would suggest a nephrotic pattern. Collagen vascular disorders often present with a constellation of symptoms, including rashes and joint involvement. Nephrolithiasis seldom if ever presents painlessly and does not usually cause persistent hypertension outside of the acute presentation. While essential hypertension can present with hematuria and proteinuria, this would be more likely in chronically elevated blood pressure.

One compelling clue in the patient's history was his occupational exposure to jet fuel over a period of 10 yr as a fuels specialist. Organic solvents and hydrocarbons have been suggested to increase the risk of chronic nephropathies.[7,12,13,16] Considering the nature of this patient's occupation before becoming an Air Force boom operator, it is worth noting the possible link of occupational exposure to jet fuel over a long duration. While direct causality has been difficult to prove, industrial solvents and organic fuels have been associated with risk for glomerular disease. In retrospective analyses and case studies from both human and animal models, hydrocarbon occupational exposures have been shown to increase the risk of developing glomerular disease through apparent immune mediated mechanisms.[10,12] It has been suggested that by combining with renal proteins, hydrocarbons may act as haptens and induce autoimmunity against kidney cells.[7]

In light of this history and because the major routes of absorption of these compounds are through the lungs and skin, you think back to your Mission Essential Tasks and Line Support Tasks. One component of this is the flight surgeon's role in occupational shop visits; these work environment walk-throughs require extra vigilance in shops that work directly with volatile hydrocarbons. This case reminds us of the importance of counseling each shop on respirator fit testing, care and use of gloves, and proper decontamination protocols of exposure events when handling solvents and fuels, further elucidating the flight surgeon's role in the execution of safe practices in the operational environment to avoid conditions that can lead to chronic disease. Another compelling finding in this patient's history was evidence of a recent upper respiratory tract infection, which also has been shown to preexist shortly before the presentation of glomerulonephritis in about 50% of cases.[2]

3. What do you do next and what is the aeromedical disposition of this airman?

A. Prepare for a transfer or aeromedical evacuation to a definitive care facility.
B. Extend DNIF; reference Air Force Waiver Guide to determine the need for a flying waiver.[4]
C. Inform and reassure your patient of both diagnosis and prognosis.
D. Follow patient's progress closely, guide referrals, and take care to document subspecialty findings for use in medical disposition.
E. All of the above.

ANSWER/DISCUSSION

3. E. All of the above; these are appropriate actions to take at this time. The diagnosis of intrinsic kidney disease requires subspecialty care and treatment. Aviators with a history of renal disease in the Air Force are categorized by their degree of proteinuria and other comorbidities, as well as renal function, to determine the need for and the approval of a flying waiver. Individuals with normal renal function who are found to have urine protein excretion of less than 200 $mg \cdot d^{-1}$ are able to return to flying without a waiver once renal function impairment and chronic nephritis have been ruled out.[4]

In this case the aviator was aeromedically evacuated out of theater to his home station, where a complete workup ensued. A persistent proteinuria was discovered of greater than 200 $mg \cdot d^{-1}$, but less than 3.5 $g \cdot d^{-1}$, in addition to persistent hypertension and paroxysmal hematuria on follow-up urine microscopy. Due to the persistent proteinuria and hematuria, a renal biopsy was performed without complication. Immunohistological staining revealed a diagnosis of immunoglobulin A (IgA) nephropathy.

IgA nephropathy is the most common cause of primary idiopathic glomerulonephritis in the developed world. Slow progression to end-stage renal disease occurs in up to 50% of affected patients, often over 20 to 25 yr. The remaining patients enter a sustained clinical remission or have a persistent low-grade hematuria and proteinuria.[2]

Clinical predictors of IgA nephropathy include elevated serum creatinine, hypertension, and persistent protein excretion above 500 $mg \cdot d^{-1}$. Patients who have recurrent episodes of gross hematuria without proteinuria are at low risk for progressive kidney disease. Patients with persistent arterial hypertension and proteinuria more than 1 $g \cdot d^{-1}$ progress more rapidly to end stage disease.[2,20]

Histological findings on renal biopsy in patients with IgA nephropathy have also been associated with an increased risk of progressive disease. These include both markers of more severe inflammatory disease such as crescent formation and immune deposits in the capillary loops in addition to the mesangial deposits that are present in all patients, and markers of chronic fibrotic disease such as glomerulosclerosis, tubular atrophy, interstitial fibrosis, and vascular disease.[19,20] The Oxford classification is a pathological classification that identifies

several variables that correlate with adverse renal outcomes, independent of clinical features, including mesangial proliferation, endo-capillary proliferation, segmental glomerulosclerosis, and tubule-interstitial fibrosis.[18–20]

The role of immunosuppresive therapy in IgA nephropathy is uncertain. Various regimens have been used, mostly consisting of anti-inflammatory doses of glucocorticoids alone or in combination with other immunosuppressive drugs. The available studies are not conclusive, since most are relatively small and have limited follow-up, and the results are sometimes conflicting. For patients with stable or slowly progressive disease, angiotensin inhibition is initiated prior to immunosuppressive therapy.[6,9] The indications for the use of glucocorticoids alone or in combination with other immunosuppressive drugs in patients with IgA nephropathy are not well defined, and one must take into account the potential toxicity of these drugs. Most nephrologists do not treat mild, stable, or very slowly progressive IgA nephropathy with glucocorticoids or other immunosuppressive therapies.[6,9]

Nonimmunosuppressive therapies are meant to slow progression of the disease. These include antihypertensives, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. In patients with proteinuria, the daily use of omega-3 fatty acids of prescription strength and quality is also indicated. Although the pathophysiology of IgA nephropathy is incompletely understood, it is likely that omega-3 fatty acid supplementation prevents renal disease progression by interfering with a number of effector pathways triggered by mesangial immune-complex deposition. Strong evidence suggests that treatment with a daily dose of omega-3 fatty acids slows the progression of renal disease in high-risk patients with IgA nephropathy. These benefits persisted after several years of follow-up.[3]

Patients with isolated hematuria, no or minimal proteinuria, and a normal glomerular filtration rate are not treated aggressively with a biopsy or identified as having IgA nephropathy. However, these patients should be monitored at 6 and 12 mo and their blood pressures monitored at more regular intervals.[2]

Thankfully, only 10% of individuals with IgA nephropathy develop nephrotic syndrome. The Air Force grants flying waivers for IgA nephropathy on a case-by-case basis. In this case, a Flying Class III waiver was granted, with close observation every 3 yr for waiver renewal and to review renal function, blood pressure, and 24-h urine protein excretion. Unrestricted waivers are not considered for this condition.[4]

The U.S. Navy disqualifies from flying duties any patient with current, or a history of, clinically significant proteinuria, unless it can be determined to be of benign nature such as orthostatic proteinuria.[11] Proteinuria and specifically glomerulonephritis is disqualifying from flying duties in the U.S. Army.[15] The Federal Aviation Administration Guide for Aviation Medical Examiners states that prior to a special issuance for any class of examination with a history of significant proteinuria, the Aviation Medical Examiner may issue the certificate only after a consideration of renal function and approval of hypertension medications.[5]

It is important to remember that the mainstay of treatment in glomerular disease is early detection and protection of further damage through pharmacological intervention and mediating the autoimmune response. Signs and symptoms are scarce, so astute observation for unique presentations of pathology such as pitting edema, gross hematuria, or abrupt elevation in blood pressure can give cause for alarm in someone with a family history or in this case a risk from a possible occupational exposure that may lead to increased suspicion for glomerular disease.

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