CLINICAL VIGNETTE

Ankylosing Spondylitis and IgA Nephropathy
A Case of Inflammatory Arthritis and Associated Glomerulonephritis

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Case

A 53-year-old man with no significant past medical history presented to primary care with right sided flank pain for 2 weeks. He was previously evaluated at an outside ER and CT Abdomen and Pelvis showed no renal stones and was otherwise normal. X-rays of the thoracic and lumbar spine showed multilevel spurring in the mid and lower thoracic spine, as well as mild lumbar spine degenerative disc disease and abnormalities at the margin of the left sacroiliac joint. His creatinine and electrolytes were normal, but a urinalysis (UA) showed 3+ blood and 1+ protein. He was given Tramadol and Cyclobenzaprine with minimal relief. His primary care doctor recommended Ibuprofen and MRI of the thoracic spine. The MRI revealed bone marrow edema in scattered thoracic vertebra with associated endplate bone marrow changes concerning for degenerative versus inflammatory arthritis. Repeat UA was ordered but not completed.

The patient was lost to follow up, but returned 6 months later with acute right ankle pain with associated joint swelling. Radiographs of the ankle and foot demonstrated no fracture, normal joint spaces, but were notable for soft tissue swelling at the medial ankle. Repeat UA demonstrated 3+ blood, 17 red blood cells per HPF, as well as 1+ protein. Creatinine was 0.96, with normal glomerular filtration rate. The patient was referred to Podiatry for suspected ankle strain and Nephrology for persistent microscopic hematuria and proteinuria.

On evaluation with Nephrology no pedal edema was noted and his exam was otherwise normal. He was instructed to stop taking NSAIDs and labs were obtained. CBC had WBC of 12.17, Hgb of 12.5 and 722k platelets. Urine protein to creatinine ratio was 1.2, with albumin to creatinine ratio of 674.6 mcg/mg. PEP showed elevated total protein, but no monoclonal bands. Serum immunoglobulins demonstrated an elevated IgA 574, elevate IgG 2410, and normal IgM. Renal Ultrasound demonstrated no hydronephrosis, renal stones or masses.

Due to patient's sub-nephrotic proteinuria as well as microscopic hematuria with preserved kidney function, glomerulonephritis was suspected and kidney biopsy was recommended. Kidney biopsy demonstrated IgA nephropathy with segmental sclerosis with no significant interstitial fibrosis or tubular atrophy and mild arteriolar sclerosis. Patient was started on Losartan for proteinuria. Systemic corticosteroids were not started given preserved kidney function.

He was seen by podiatry for ongoing ankle pain and swelling. Magnetic Resonance Imaging (MRI) of the ankle showed tenosynovitis of the tibialis posterior and flexor hallicus longus, tibiotalar effusion, as well as reactive bone marrow edema of the medial malleolus. He was treated by podiatry for suspected ankle sprain with cast immobilization. Despite 6 weeks of casting the patient's symptoms did not improve. He was later referred to Rheumatology to evaluate for possible inflammatory arthritis.

Rheumatology exam showed right ankle synovitis with swelling and tenderness to palpation, most notable at the medial aspect consistent with posterior tibial tenosynovitis. There was also synovitis of the right first Metatarsalphalangeal joint. There was concern for inflammatory arthritis, crystalline arthritis and septic arthritis. Ultrasound guided ankle aspiration with synovial analysis demonstrated no crystal and negative gram stain and bacterial culture. Cell count showed RBC 6,000 and WBC 281, Neutrophils 17%, Lymphocytes 14%, Monocytes 69%.

Serologies were negative for rheumatoid factor and anti-cyclic citrulinated peptide. Erythrocyte sedimentation rate (ESR) was 108 and C-Reactive Protein (CRP) was 3.7 (normal less than 0.8). Human Leukocyte Antigen (HLA)- B27 was positive. On follow up evaluation patient, reported ongoing pain and swelling of the right ankle and right great toe. He also had a return of low back pain. Exam demonstrated tenderness to palpation of the bilateral sacroiliac joints. He also recalled that his father had a diagnosis of Reiter's Syndrome, otherwise known as Reactive arthritis, at sub-type of Spondyloarthritis.

A diagnosis of HLA B27 positive Ankylosing Spondylitis with peripheral arthritis was given. The patient had already failed treatment with Non-steroidal anti-inflammatory drugs (NSAIDs) and was started on Adalimumab 40mg subcutaneous injection every 14 days. Eight weeks into treatment, his ankle and foot pain improved significantly and his back pain had resolved. The patient's proteinuria from IgA nephropathy also resolved after treatment with Losartan.

Discussion

Renal involvement in Ankylosing Spondylitis has been well described, and can occur in many forms, including secondary

amyloidosis, NSAID induced nephropathy and IgA nephropathy. IgA nephropathy has been associated with ankylosing spondylitis, but the pathogenesis is unknown. Patients with AS can have increased circulating levels of IgA and IgA containing immune complexes, which are over produced by B cells. The proposed multi step model of pathogenesis has elevated level of circulating IgA infiltrate the mesangium which subsequently activates complement and mesangial growth factors, resulting in mesangial proliferation and glomerulonephritis.

The "Multi Step Model" has elevated circulating levels of abnormal IgA that are galactose-deficient.[6] The galactose deficient IgA (Gd-IgA1) may be produced due to genetic factors resulting in mis-trafficking of B cells from mucosal to systemic compartments. Antibodies are then directed against Gd-IgA1, which can be of IgA or IgG sub-class. These Immune complexes then get deposited in the kidney either from the circulation or get formed in situ at the site of deposition of Gd-IgA1.[7] The deposited immune complexes then activate a complement cascade and induce mesangial cell proliferation, matrix deposition, and activation all leading to kidney damage. This can happen with any systemic or immunologic disorder.

IgA nephropathy can present as episodic gross hematuria, asymptomatic microscopic hematuria and proteinuria (like in our patient), nephrotic syndrome, slowly progressive chronic kidney disease or rapidly progressive glomerulonephritis (RPGN). Poor prognostic indicators in IgA Nephropathy are proteinuria >1 gm /day, worsening hypertension, serum creatinine greater than 1.5, kidney biopsy with greater degree of fibrosis and atrophy.[8] Additionally, the risk of kidney impairment is increased with high disease activity or elevated inflammatory indicators such as CRP or ESR.[9]

In secondary causes of IgA nephropathy, treatment of the primary etiology is the mainstay of treatment. Standard treatment for Ankylosing Spondylitis involves use of NSAIDs, which should be avoided in IgA Nephropathy. Treatment with Tumor Necrosis Factor (TNF) inhibitors are often next line treatments of Ankylosing Spondylitis and can be highly effective in controlling disease activity and preventing degenerative changes. Interestingly, previous studies have found that use of TNF inhibitors to treat patients with AS, have no influence on renal prognosis in cases with associated IgA Nephropathy.[10] As a result, in these cases general treatment of IgA Nephropathy is initiated, which involves blood pressure control as well as reduction of proteinuria with renin angiotensin system inhibition. Corticosteroids are only used in patients with high risk of progression to end stage renal disease.

In the case described IgA level was elevated. Acute phase reactants including the ESR and CRP were also elevated. The proteinuria was treated successfully with the use of an angiotensin receptor blocker, and his inflammatory joint pains were well controlled with a TNF inhibitor. It is likely the patient has had subacute symptoms of ankylosing spondylitis for months to years before he presented to the medical system.

Conclusion

This case demonstrates the association of IgA Nephropathy with Spondyloarthritis. It is important to recognize this association, as well as other renal manifestations associated with Spondyloarthritis for timely diagnosis and treatment.

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