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REVIEW ARTICLE

Hydralazine-induced pauci-immune glomerulonephritis: intriguing case series with misleading diagnoses

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Hydralazine has been used since the 1950s for the management of hypertension. Evidence for hydralazine-associated vasculitis dates to pre-ANCA (antineutrophil cytoplasmic antibodies) era. This abstract describes two cases of ANCA-positive pauci-immune glomerulonephritis (GN) in challenging scenarios where diagnosis was misconstrued. A comprehensive literature review was done to understand the pathogenesis of drug-induced pauci-immune GN. We have described key diagnostic features that are helpful in distinguishing idiopathic ANCA vasculitis from drug-induced vasculitis. Additionally, we have also described different treatments meant to provide therapy options with the least side effects.

Keywords: *hydralazine*; *renal limited*; *pauci-immune GN*

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Hydralazine-associated vasculitis falls under the category of drug-induced vasculitis, which includes other medications like antibiotics, antithyroid medication, and levamisole-adulterated cocaine (1, 2). Drug-induced vasculitis is commonly misdiagnosed because of significant overlap of diagnostic features with idiopathic vasculitis. Clinically, the disease manifestations are sometimes restricted to a single organ; however, in most cases multiple organs are affected. We have described two challenging cases of hydralazine-induced pauci-immune glomerulonephritis which were initially misdiagnosed as acute tubular necrosis and acute interstitial nephritis, respectively.

Case 1

An 82-year-old African American female was brought to the ER after she was found lying in her bed for 3 days. At the time of presentation, she was weak and difficult to arouse. Initial history was obtained from the family. She had a medical history of diabetes mellitus, hypertension, and hyperlipidemia. There was no family history of renal or autoimmune disease. There was no history of preceding symptoms including rashes, arthralgia, or recent weight loss. Medications included candesartan 32 mg daily, hydrochlorothiazide 12.5 mg daily, atenolol 50 mg daily, and hydralazine 25 mg twice daily. Physical examination concluded significantly sunken eyes, dry mouth, and poor skin turgor but no skin rash. Cardiac exam: irregular rhythm, normal heart sounds, no additional murmurs or gallop rhythm. Respiratory: poor inspiratory effort, air entry equal on both sides. CNS: lethargy, slow speech, and intermittent confusion but no asterixis. Vital signs on admission: BP 140/60, RR 12, pulse 50, and Tmax 36.5°C. Metabolic panel on initial presentation was significant for Na 151 meq/dl, K 6.4 meq/dl, HCO_3 13.2 meq/dl, blood urea nitrogen 212 mg/dl, and creatinine 19.7 mg/dl. Her baseline creatinine was later found to be 1.1 mg/dl from the outpatient blood workup six months ago. Complete blood count: WBC 5.94 cmm, Hb 9.5 g/dl, HCT 31%, and platelet count 101 cmm. Urinalysis showed +1 protein, +4 heme, and +1 ketones. On microscopic analysis, numerous red blood cells and few RBC clumps, and 0–3 white cells were seen, although no cast was seen. Urine sodium was 14meq/dl, FeNa was 1.13%, and spot protein to creatinine ratio was 465 mg/g. The renal sonogram showed the right kidney to be 11 cm and the left kidney to be 10.8 cm. Slight increase in attenuation of the kidneys was suggestive of medical renal disease. Bilateral echogenic masses were later confirmed as angiomyolipoma by CT scan. Initial management included hydration with hypotonic bicarbonate infusion followed by hemodialysis. Provisional diagnosis was ATN secondary to severe dehydration. Her mental status improved after several dialysis sessions; however, she remained oliguric and dialysis dependent. Repeat urine studies showed spot protein/creatinine ratio of 2 g. Serology for

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autoimmune disease was significant for an anti-nuclear antibody (ANA) titer of 1:1,280 in a homogeneous pattern (n = undetectable), and mild elevation in phosphatidylserine Ig M, anti-cardiolipin IgM, and anti-histone antibodies. Anti-double stranded (anti-dsDNA), Ig G, Ig A, and C3 and C4 complement levels were within normal limits. Hepatitis B and C serology was negative. On renal biopsy, 2 out of 14 glomeruli showed crescentic necrotizing inflammation, 3 glomeruli showed cellular crescent, and global sclerosis was found in 4 out of 13 glomeruli (Fig. 1). Immunofluorescence studies showed trace staining for Ig M and C3 but no immune complex and light chain deposits. After the biopsy results, the specimen for anti-neutrophilic cytoplasmic antibodies (ANCA) was drawn. The myeloperoxidase antibody (MPO) titer was found to be greater than 800 AI ($n \leq 1$), Proteinase-3ANCA antibody (PR3 ab) <1 and anti-histone ab was moderately positive at 2.3 U ($n \leq 1$). The final diagnosis was hydralazine-induced ANCA vasculitis with pauci-immune glomerulonephritis. After careful review of old medical records, the patient was found to be taking hydrazine for several years. After the confirmatory diagnosis, she was started on pulse dose steroids with IV methylprednisolone 250 mg TID for 3 days followed by IV cyclophosphamide 50 mg daily. Five sessions of plasmapheresis were done as part of induction therapy. However, medical therapy had to be discontinued after 1 week due to severe complications including line infection, cytomegalovirus infection, and steroid psychosis. She remained dialysis dependent and ultimately was transferred to hospice due to multi-organ failure.

Case 2

An 81-year-old Caucasian female presented to the emergency room with several days of shortness of breath associated with intermittent dry cough and decline in urinary frequency. She gave a history of diabetes mellitus type 2, HTN, HLD, hypothyroidism and heart failure with preserved ejection fraction. She had no prior history of renal disease. Review of system was negative for weight

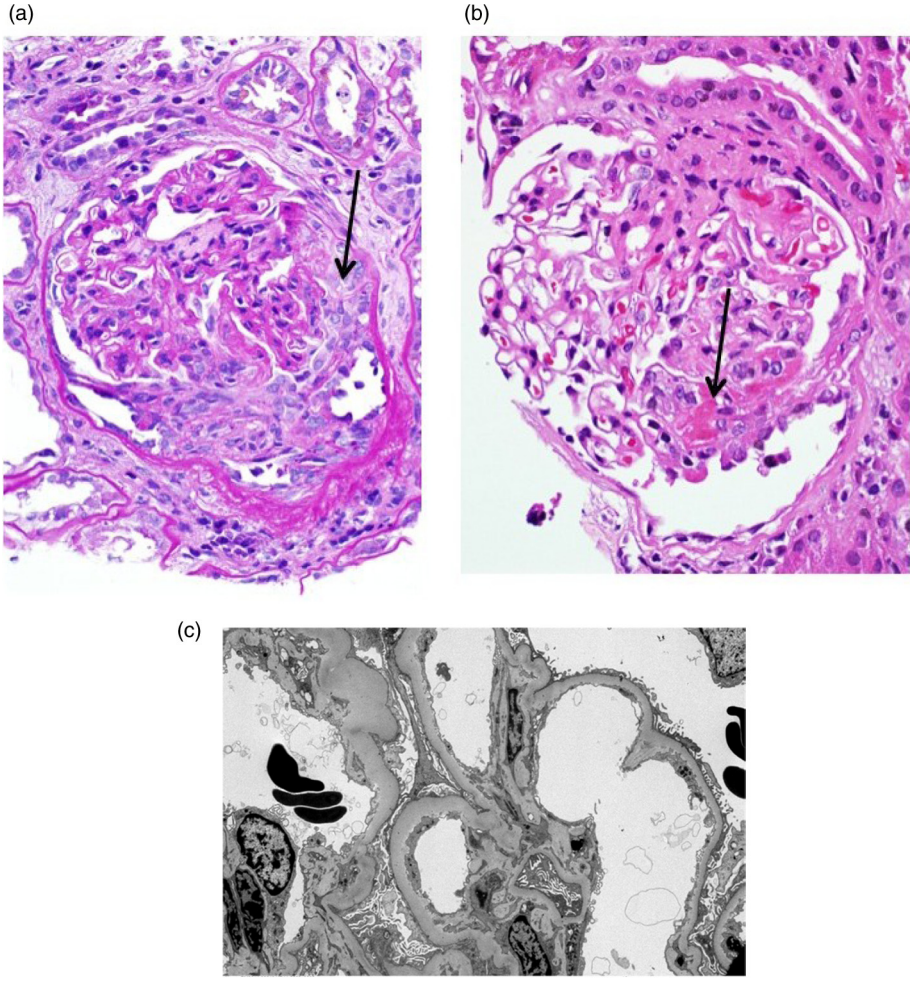

Fig. 1. Light microscopy: (a) glomeruli shows cellular crescents; (b) glomeruli shows segmental necrotizing lesion; (c) EM: focal podocyte foot process effacement, no deposits, no tubuloreticular inclusions.

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Table 1. Serological marker difference between idiopathic AAV and drug-induced ANCA vasculitis

	Drug-induced AAV	Idiopathic AAV
ANCA	Common[a]	Common[b]
Antilactoferrin ab	Common	Rare
Antihistone ab	Common	Absent
Antielastase ab	Common	Rare
Antiphospholipid ab	Common	Rare
Immune complex	Rare	Absent

Ab = antibodies, AAV = ANCA-associated vasculitis. [a]Multispecific, particularly myeloperoxidase antibodies; [b]single ANCA specificity.

loss, arthralgia, skin rashes, or hematuria. Home medications included carvedilol 12.5 mg twice daily, hydralazine 100 mg thrice daily, pantoprazole 40 mg daily, amlodipine 10 mg daily, atorvastatin 40 mg daily, apixaban 2.5 mg twice daily. Vital signs on admission: BP 180/70 mm Hg, pulse 70 bpm, and oxygen saturation 99% on room air. Physical exam: skin turgor was normal. HEENT: mucous membranes were moist. Pupils were equal, reactive to light and accommodation. Neck: supple without adenopathy. JVD was difficult to assess due to her size. Lungs: On auscultation, minimal rales at the bases. Cardiac exam showed a regular rate and rhythm. Extremities: 1+ edema. Metabolic panel depicted serum bicarbonate of 17 meq/dl, Na 139 meq/dl, K 3.9 meq/dl, BUN 68 mg/dl, and creatinine 2.7 mg/dl (baseline 1.1 mg/dl). The other findings on chemistry panel includes proBNP of 1500, Normal transaminases, CPK 57, and troponin I less than 0.3. Total protein was 8.0 with an albumin of 3.6. WBC 10.8 cmm, with a hemoglobin of 9.7 g/dl. Platelets were normal at 234,000 cmm. Serum compliment levels were normal. Serology was negative for hepatitis B, hepatitis C, and rheumatoid factor (RF). Urinalysis results showed specific gravity of 1.010, PH of 5, 1+ protein, and large occult blood. On microscopic examination: 4 to 10 red cells, 0 to 3 white cells, few urates, moderate bacteria were seen. Protein to creatinine ratio showed 2 g of protein. Renal imaging showed normal kidneys. The right kidney measured 10.5 cm in length and the left kidney measured 11.2 cm in length. Neither kidney was hydronephrotic, and no solid renal masses or calculi could be identified. She had a brisk diuresis of 800 ml following urinary catheterization. A provisional diagnosis of obstructive acute renal failure in the setting of autonomic bladder dysfunction was made. However, her creatinine did not improve. Further testing including protein electrophoresis and immunofixation was normal. A renal biopsy was done, as the etiology of her renal failure was unclear. The initial biopsy was consistent with interstitial inflammation concerning for acute interstitial nephritis. Based on the biopsy, several medications were discontinued which included amlodipine, apixaban, torasemide, carvedilol, and atorvastatin. On her follow-up visit to nephrology clinic, she complained of persistent

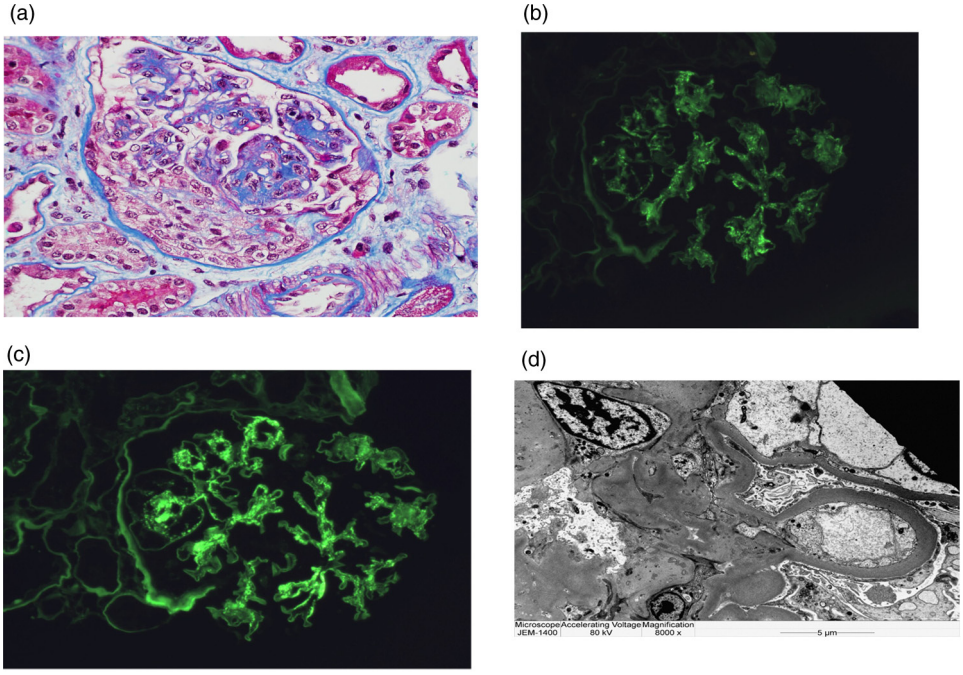

Fig. 2. Light microscopy: (a) glomeruli shows cellular crescents; (b) IF: glomeruli with trace IgM mesagnial deposits; (c) glomeruli with trace IgG mesangial deposits; (d) EM: GBM thickening, FPE effacement, and absent deposits on capillary & mesangium.

Table 2. Treatment strategies in hydralazine-induced pauci-immune GN

	Indication	Duration of therapy	Comments
Pulse dose steroids (Methylprednisolone).	Systemic disease involving two or more organs Diffuse crescentic and necrotizing inflammation proved on renal biopsy	Used for 3 days	No strong evidence regarding efficacy
Prednisone	Used in moderate-to-severe disease process Used as induction therapy	4–8 weeks. Followed by gradual taper over 6–12 months (12)	Total duration of therapy is unclear Long-term treatment, more than 1 year is rarely required for drug-induced Pacui-immune disease (13)
Immunosuppressive agents			
Cyclophosphamide CYP	Used as adjuvant to steroids to induce remission in moderate-to-severe localized or systemic disease of any severity	Unclear duration of treatment in drug-induced pauci-immune GN	IV Pulse dose CYP appear to be less toxic but equally efficacious compared with oral therapy (14) Disease course of drug-induced AAV is not as severe as primary AAV. It may be a preferred modality than oral therapy with less rate of Leukopenia (14)
Mycophenolate	Used as an adjunct to steroids	Unclear duration	Better side effect profile Alternative to CYP in drug-induced vasculitis due to less toxicity and lower rate of infections (15)
Methotrexate MTX	Used as an adjunct in mild localized disease		Not indicated in severe renal failure due to enhanced toxicity (16, 17)
Plasma exchange PE	1) Life-threatening pulmonary hemorrhage 2) Rapidly worsening kidney functions and dialysis-dependent renal failure at the time of presentation 3) Concurrent anti-glomerular basement membrane antibody disease	7 plasma exchange sessions for 14 days	Shown to reduce the progression toward ESRD compared with IV methylprednisolone alone Not shown to reduce mortality (18)
Aziothiprine AZA	Used as maintenance therapy	Duration of therapy is 6–12 months in primary AAV	AZA is shown to be superior to MMF to prevent relapse (19)
Biological agents			
Rituximab RTX	Recommended as an adjunct with steroids in primary AA, or if CYP is contraindicated. No strong evidence of its use in drug-induced pauci-immune disease Total duration of therapy is unclear. Long-term treatment, more than one year is rarely required for drug induce Pacui-immune disease (13)	Used as a part of induction therapy or In relapse state	RTX, along with steroid, is equally effective with less side effects as compared with CYP and steroids (20)

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shortness of breath and swelling in her leg. Her kidney function continued to decline, and serum creatinine increased to 4.3 mg/dl compared with 2.6 mg/dl on discharge. Final biopsy results showed evidence of glomerulonephritis as 1 out of 13 glomeruli revealed crescentic inflammation. Vasculitis workup was sent, and it was positive for anti-nuclear antibody titers greater than 1:640 in homogenous pattern, myeloperoxidase antibodies 1:460 AI ($n \leq 1$), and negative for Anti-ds DNA and anti-PRc-3. The patient was readmitted for immunosuppressive therapy and started on pulse dose steroids with IV methylprednisolone 250 mg TID for 3 days. Medications were reviewed, and hydralazine was stopped. The patient's creatinine improved in the next several days, her urine output increased, and she was discharged home on oral prednisone 60 mg daily with the diagnosis of hydralazine-induced pauci-immune GN. On discharge, the patient's serum creatinine was 2.8 mg/dl and BUN was 76 mg/dl which further improved to serum creatinine of 1.7 mg/dl and BUN of 56 mg/dl on follow-up clinic visits after 3 months. She is currently dialysis independent and on a small dose of 20 mg oral prednisone.

Discussion

Pauci is derived from the Latin word *paucus* which means little or few. Historically, it has been described as a form of glomerulonephritis with no evidence of linear immunoglobulin deposition, or immune complex deposits in patients with rapidly progressive glomerulonephritis (3). Hydralazine has been reported to cause vasculitis, particularly pauci-immune GN. A detailed review of the literature through PubMed index showed numerous studies that described various features of drug-induced vasculitis including epidemiology, clinical presentation, serological features, and treatment options (4–6). One study reported 68 cases of hydralazine-induced ANCA vasculitis. The disease was found to be prevalent in older females. The mean drug exposure was 4.7 years. The kidney was the primary organ affected followed by lungs, skin, and nerves (4). Patients with pauci-immune GN usually present with rapidly progressive glomerulonephritis with features of brown colored urine suggesting hematuria. Other features include proteinuria and renal insufficiency (7). The extra-renal manifestation of systemic vasculitis syndrome includes non-specific symptoms of fever, malaise, arthralgia, myalgia, and weight loss. Other organ-specific complications such as pulmonary hemorrhage, purpuric rash, livido reticularis, neuropathy, and retinitis can be seen with severe systemic disease (4).

The pathogenesis of hydralazine-induced pauci-immune glomerulonephritis is unclear. One hypothesis is that hydrazine accumulates in neutrophils, binds to myeloperoxidase granules (MPO), and induces cytotoxic products formation that lead to neutrophil apoptosis. The cellular apoptosis in the absence of priming, leads to the expression of ACNA antigen on cellular surface, and hence ANCA formation (8). The presence of multi-antigenicity in drug-induced vasculitis is explained by the alteration in molecular configuration of MPO granules by hydralazine, consequently inducing the autoimmune response to other neutrophilic proteins (including lactoferrin, elastase, and nuclear antigen), thereby rendering them immunogenic (9). Jiang et al. suggested the role of T cells in stimulating the immune response. It is proposed that cytotoxic products formed as a result of neutrophilic activation by MPO granules and conversion of drugs into cytotoxic agents are immunogenic for T cells. Activated T cells then induce B cells to produce ANCA (10).

The rarity of drug-induced ANCA vasculitis and overlapping features with idiopathic vasculitis is the greater challenge in early diagnosis. The diagnosis mainly relies on constitutional symptoms, including organ-specific symptoms, detailed medication history, the total duration of drug therapy, the presence of various antibodies, and the resolution of symptoms after discontinuation of the offending agent. Since multi-antigenicity is a key feature, various serological markers aid in diagnosing drug-induced pauci-immune GN (Table 1). Another distinct characteristic of drug-induced pauci-immune GN is the presence of very high myeloperoxidase (MPO) antibody titers (11).

A kidney biopsy is strongly encouraged for definitive diagnosis of acute kidney injury and to ascertain the severity of disease. Typical biopsy in patients with drug-induced ANCA-associated vasculitis (AAV) shows necrotizing and crescentic inflammation (Fig. 1). Interstitial nephritis and significant tubular damage is seen on some occasions. A small subset of patients also had subacute disease characterized by glomerular fibrosis, either alone or accompanied by an active focal disease with necrosis and crescent formation (4).

No randomized trial looked at the ideal treatment for drug-induced pauci-immune GN. Treatment must be individualized based on the severity of the disease, age, co-morbid conditions, and entry time serum creatinine. Treatment options vary from discontinuing the offending agent alone, to the use of immunosuppressive therapies including steroids (Fig. 2, Table 2).

Conclusion

Hydralazine-induced pauci-immune GN is a rare form of anti-neutrophilic antibody associated vasculitis. There is still a diagnostic dilemma because of rarity of the condition and significant overlap with idiopathic ANCA vasculitis. We highlighted some essential features related to drug-induced pauci-immune GN that can potentially help with early diagnosis and better management of the patients with this disease. Early detection of myeloperoxidase antibody with several other serological markers can aid in diagnosing the disease. An early renal biopsy is essential

to guide the treatment course. Offending agent must be stopped early. Immunosuppression should be individualized, the regime with less side effects and a shorter duration is preferred. As the disease has a mild course, long-term maintenance therapy may not be required if the offending medication is discontinued early (13).

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References

1. Hogan JJ, Markowitz GS, Radhakrishan J. Drug-induced glomerular disease: Immune-mediated injury. Clin J Am Soc Nephrol 2015; 10: 1300–10.
2. Carlson AQ, Tuot DS, Jen KY, Butcher B, Graf J, Sam R, et al. Pauci-immune glomerulonephritis in individuals with diseased associated with levamisole-adulterated cocaine. Medicine 2014; 93: 290–7.
3. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994; 37(2): 187–92.
4. Yokogawa N, Vivino FB. Hydralazine-induce autoimmune deposition: Comparison to idiopathic lupus and ANCA-positive vasculitis. Mod Rheumatol 2009; 19: 338–47.
5. Almorth G, Ensetrom S, Hed J, Sameulson I, Sjostrom P. Autoantibodies to leucocyte antigens in hydralazine-associated nephritis. J Inter Med 1992; 231: 37–42.
6. Cambridge G, Wallace H, Brenstein RM, Leaker B. Autoantibodies to idiopathic and drug induced SLE and vasculitis. Br J Rheumatol 1994; 33: 109–14.
7. John R, Herzenberg AM. Renal toxicity of therapeutic drugs. J Clin Pathol 2009; 62: 505–15.
8. Denissen NH, Peters JG, Masereeuw R, Barrera P. Can sulfasalazine therapy induce or exacerbate Wegener's granulomatosis? Scand J Rheumatol 2008; 37: 72–4.
9. Bonaci-Nikolic B, Nikolic MM, Andrejevic S, Zoric S, Bukilica M. Antineutrophil cytoplasmic antibody (ANCA)- associated autoimmune diseases induced by antithyroid drugs: Comparison with idiopathic ANCA vasculitides. Arthritis Res Ther 2005; 7: 1072–81.
10. Jiang X, Khursigara G, Rubin RL. Transformation of lupus-inducing drugs to cytotoxic products by activated neutrophils. Science 1994; 266: 810–13.
11. Choi HK, Merkel PA. Drug-Associated antineutrophilic cytoplasmic antibody-positive vasculitis. Arthritis Rheum 2000; 43: 453–13.
12. Gao Y, Zhao MH. Drug-Induced anti-neutrophilic cytoplasmic anti-body associated vasculitis. Nephrology 2009; 14: 33–41.
13. Goa Y, Chen M, Ye H, Yu F, Guo XH, Zhao MH. Long term outcomes of patient with propylthiouracil-indued anti-neutrophilic cytoplasmic auto-antibody-associated vasculitis. Rheumatology 2008; 47: 1515–20.
14. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized trial. Ann Intern Med 2009; 150(10): 670–80.
15. Hu W, Liu C, Xie H, Chen H, Liu Z, Li L. Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involvement. Nephrol Dial Transplant 2008; 23(4): 1307–12.
16. de Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005; 52(8): 2461–9.
17. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007; 18(7): 2180–8.
18. Walsh M, Casian A, Flossmann O, Westman K, Höglund P, Pusey C, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int 2013; 84(2): 397–402.
19. Hiemstra TF, Walsh M, Mahr A, Savage CO, De Groot K, Harper L, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody associated vasculitis: A randomized controlled trial. JAMA 2010; 304: 2381–8. doi: http://dx.doi.org/10.1001/jama.2010.165822
20. Jones R, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab vs cyclophosphamide for ANCA-associated renal vasculitis. N Engl J Med 2010; 363: 211–20.