

Case Series

A Case Series Study to Assess Body Mass Index in Patients' with ANCA Associated Vasculitis

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Abstract

Background: Vasculitis is an inflammatory process of the blood vessels, and is characterized histo-pathologically by inflammation and fibrinoid necrosis of the vessel wall. ANCA associated vasculitis follows a relapsing-remitting time course and accounts for considerable morbidity and mortality. The extensive renal injury that occurs often leads to end stage renal failure. The aim of this study was to investigate if body mass index has any relation to ANCA associated vasculitis, severity of disease presentation and if the distance from the biopsy center plays a role.

Methods: We retrospectively reviewed charts of patients who had an international classification of diseases diagnosis of ANCA vasculitis and presented at Ruby Memorial Hospital-West Virginia University (Morgantown, West Virginia) between 2002 and 2013.

Results: 11 patients (50%) were overweight while 16 patients (72.7%) had a body mass index greater than 25. Overall 13 patients (59%) were MPO positive. Of these, 9 patients (69.2%) were either overweight or obese, while of the patients with PR3 positivity, 7 patients (77.8%) were either overweight or obese. Out of the 22 patients who presented with AAV only 7 patients (31.8%) resided within a 10 mile radius of the biopsy center, while 15 patients (68.2%) resided more than 10 miles from the biopsy center of the 9 patients with greater than 50% crescents on their biopsy 4 needed renal replacement therapy and 4 needed therapeutic plasma exchange.

Conclusion: Our results showed a predominantly overweight or obese population. Our results suggested a high prevalence of being either overweight or obesity in patients with PR3 as compared to MPO. Increased distance from the biopsy center did relate to an increased severity of disease at initial presentation. Further studies

are required to determine if increased body mass index is a risk factor for the development of ANCA associated vasculitis.

Keywords: ANCA vasculitis; Anti-neutrophil cytoplasmic antibody; C-ANCA; MPO; Obesity; Overweight; P-ANCA; PR3; Renal replacement therapy; Therapeutic plasma exchange

Introduction

Vasculitis is an inflammatory process of the blood vessels, and is characterized histo-pathologically by inflammation and fibrinoid necrosis of the vessel wall. Inflammation may occur in the walls of veins, arteries and/or capillaries. Depending on the size and location of the affected vessels, the clinical presentation of the patients varies. Within the group of vasculitides, there is a distinct subgroup characterized by the presence of necrotizing lesions of small vessels and the regular presence of Antibodies against Cytoplasmic Antigens in neutrophils (ANCA) and therefore are grouped together as ANCA Associated Vasculitis (AAV) [1]. According to the International Chapel Hill Consensus Conference (CHCC) on the nomenclature of vasculitides AAV can be categorized into the following types: (i) Microscopic Polyangiitis (MPA), (ii) Granulomatosis with Polyangiitis (GPA, formerly called Wegener's granulomatosis), (iii) Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly Churg-Strauss syndrome) and (iv) Renal Limited Vasculitis (RLV) or idiopathic Rapidly Progressive Glomerulonephritis (RPGN) [2]. AAV affects small to medium sized vessels and is characterized by the presence of Anti-Neutrophil Cytoplasmic Antibodies (ANCA) with specificity for either Proteinase-3 (PR3) or Myeloperoxidase (MPO). ANCA positive patients usually have either PR3-ANCA or MPO-ANCA. The occurrence of both complexes in an individual patient is extremely rare. Antibodies against PR3 (anti-PR3) are predominantly found in patients with active GPA, while MPO antibodies occur more frequently in patients with RLV [3]. Absence or paucity of immune complex deposits in the vessel walls is very characteristic, hence the name 'pauci immune vasculitis' [4].

Vasculitides cause severe morbidity and increase mortality due to vascular obstruction with tissue ischemia and infarction of several organ systems [5,6]. AAV follow a relapsing-remitting time course and account for considerable morbidity and mortality. The extensive renal injury that occurs often leads to end stage renal failure. Rapidly progressive deterioration of renal function is a frequent but clinically unfavorable feature of Anti-Neutrophil Cytoplasm Autoantibody (ANCA) associated vasculitis, including microscopic polyangiitis, Wegener's granulomatosis, and renal limited vasculitis [7].

In the United States, GPA affects an estimated 30000 people while MPA affects 10000 people. There are approximately 2600 new cases of GPA and 900 new cases of MPA annually in the United States [8]. West Virginia now has the second highest adult obesity rate in the United States according to the state of obesity: better policies for a healthier America. West Virginia's adult obesity rate is 35.7% up from 23.9% in 2000 and from 13.7% in 1990. As per the data the obesity rate is highest at 40.2% in the 45-64 year age group and affects 34.7% whites. Meanwhile there is no significant difference in distribution based on gender. Obesity is a medical condition in which excess body

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fat has accumulated. The Body Mass Index (BMI) which is calculated by dividing the persons' weight by the square of their height is used when referring to patients especially those that are obese. Overall BMI is divided into three categories (i) normal weight (BMI 18.5-24.9), (ii) over weight (BMI 25-29.9) and (iii) obese (BMI 30 +), however some people prefer to further categorize obesity into obese (BMI 30-34.9), severely obese (BMI 35-39.9) and morbidly obese (BMI 40+).

The aim of this study was to investigate if the BMI at the time of initial hospitalization has any relation to ANCA associated vasculitis, the severity of disease at presentation and if the distance from the biopsy center plays a role in this. To date there are no studies that have reported on the BMI of patients diagnosed with ANCA associated vasculitis. This paper presents biopsy-based case series of patients with AAV. For markers of severity of disease we used the need for Renal Replacement Therapy (RRT) and Therapeutic Plasma Exchange (TPE) occurrence during the initial hospitalization.

Materials and Methods

We retrospectively reviewed charts of patients who had an International Classification of Diseases (ICD) diagnosis of ANCA vasculitis and presented at Ruby Memorial Hospital-West Virginia University (Morgantown, West Virginia) between 2002 and 2013. Prior to conducting the chart review approval was obtained from the Internal Review Board (IRB). A total of 50 patients were found to have an ICD diagnosis code corresponding to ANCA Associated Vasculitis (AAV); however complete charts with verification of the diagnosis was found on only 22 based on the electronic medical records. Thus for our case series we reviewed only these 22 charts. Renal biopsy was performed in all 22 patients. All patients had ANCA serology testing. The inclusion criteria was patients who are 18 years of age and older at the time of biopsy and had a diagnosis of AAV. The following information was collected on all the patients: age, gender, BMI (at the time of initial hospitalization), home zip codes, ANCA serology, histology report, need for RRT, need for TPE, admission blood urea nitrogen and creatinine value. Exclusion criteria was patients less than 18yrs of age. For our study initially we identified all the 5 categories of BMI that is (i) normal weight (BMI 18.5-24.9), (ii) over weight (BMI 25-29.9), (iii) obese (BMI 30-34.9), (iv) severely obese (BMI 35-39.9) and (v) morbidly obese (BMI 40+); however for the analysis and reporting of the results we combined and referred to all those with a BMI of greater than 30 as obese.

The primary outcome was to see if the patients' BMI had any relation with AAV and the severity of disease at presentation. We used the need for Renal Replacement Therapy (RRT) as a marker for severity of disease. Since TPE is a treatment modality that is applied in patients with severe kidney injury or pulmonary symptoms, we also used that as an indirect marker for disease severity. Secondly, we looked at if the distance from the biopsy center had any relation with disease severity. Does a delay in conducting a biopsy and reaching the diagnosis due to increased distance from a biopsy center correspond with increased disease severity such as the need for RRT and TPE?

Results

In our case series of 22 patients the mean age was 56 yrs (range: 20-74yrs) with 50% of the sample being males. All 22 patients (100%) were Caucasian. 6 patients (27.3%) were elderly (greater than 65 yrs). 9 patients (40.9%) had an underlying diagnosis of hypertension prior to presentation (Table 1). Upon review of the results 11 patients (50%) were overweight while 6 patients (27.3%) were obese (BMI equal to

or greater than 30) and 16 patients (72.7%) had a BMI greater than 25 (Figure 1). Overall 13 patients (59%) were MPO positive. Of the patients with MPO positivity, 9 patients (69.2%) were either overweight or obese, while of the patients with PR3 positivity, 7 patients (77.8%) were either overweight or obese (Figure 2).

Characteristics	n/percentage
Age (average)	56.77
Sex	
Female	11/ 50%
Male	11/ 50%
Race	
White	22/ 100%
History of	
DM	6/ 27.2%
HTN	9/ 40.9%
CAD	1/ 4.5%
Weight	
Normal BMI (18.5-24.9)	5/ 22.7%
Overweight (25-29.9)	11/ 50%
Obese (30-34.9)	3/ 13.6%
Severely obese (35-39.9)	1/ 4.5%
Morbidly obese (40+)	2/ 9%
Distance from Biopsy Center	
Within 10 miles	7/ 31.8%
11 to 50 miles	9/ 40.9%
51 to 100 miles	4/ 18.1%
100+ miles	2/ 9%
ANCA type	
c-ANCA/ PR3	9/ 40.9%
p-ANCA/ MPO	13/ 59.1%
Treatment	
Renal replacement therapy	7/ 31.8%
Therapeutic plasma exchange	7/ 31.8%

Table 1: Characteristics of the Cohort.

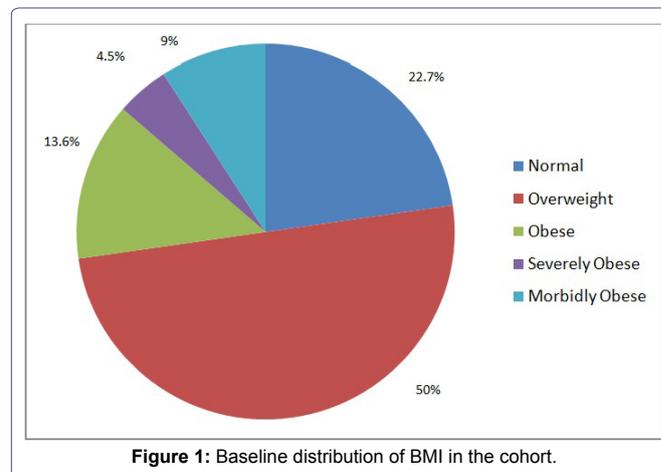


Figure 1: Baseline distribution of BMI in the cohort.

Out of the 22 patients who presented with AAV only 7 patients (31.8%) resided within a 10 mile radius of the biopsy center, while 15 patients (68.2%) resided more than 10 miles from the biopsy center

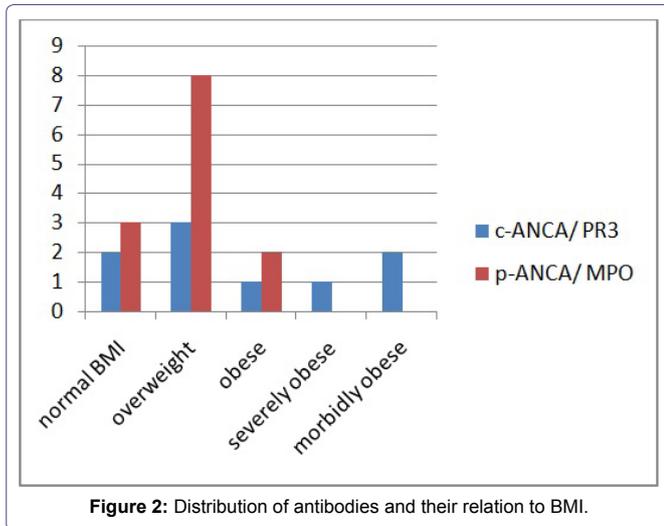


Figure 2: Distribution of antibodies and their relation to BMI.

(Figure 3 and 4). Of these 15 patients being more than 10 miles away from the biopsy center, 7 patients (46.7%) had greater than 50% crescents found on their biopsy and 3 patients (20%) needed RRT while 4 patients (26.7%) needed TPE as part of their treatment regimen.

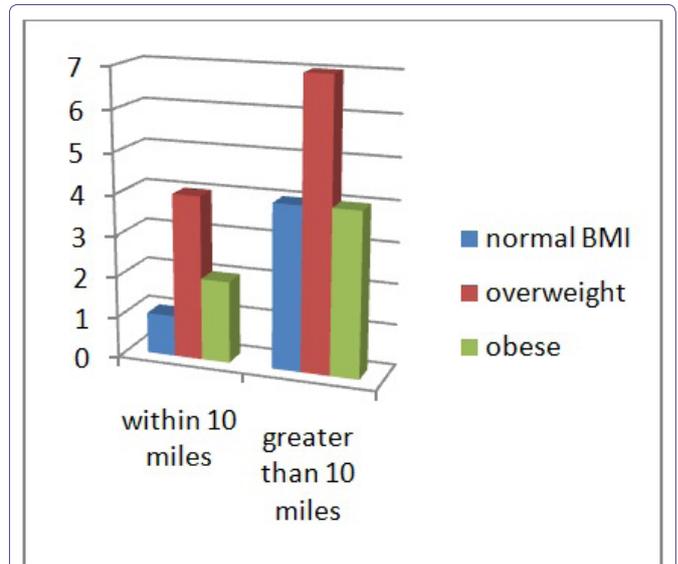


Figure 4: Distribution of BMI relative to the distance from the biopsy center.

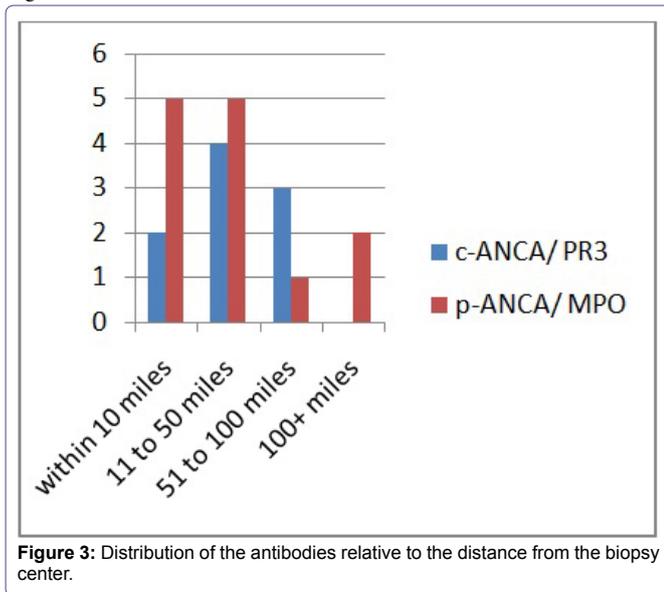


Figure 3: Distribution of the antibodies relative to the distance from the biopsy center.

In our overall sample 7 patients (31.8%) needed RRT and 7 patients (31.8%) needed TPE. Of the 7 patients who needed RRT, 2 patients (28.6%) were overweight and 3 patients (42.9%) were obese. Meanwhile of the 7 patients who needed TPE, 2 patients (28.6%) were overweight and 4 patients (57.1%) were obese (Figure 5).

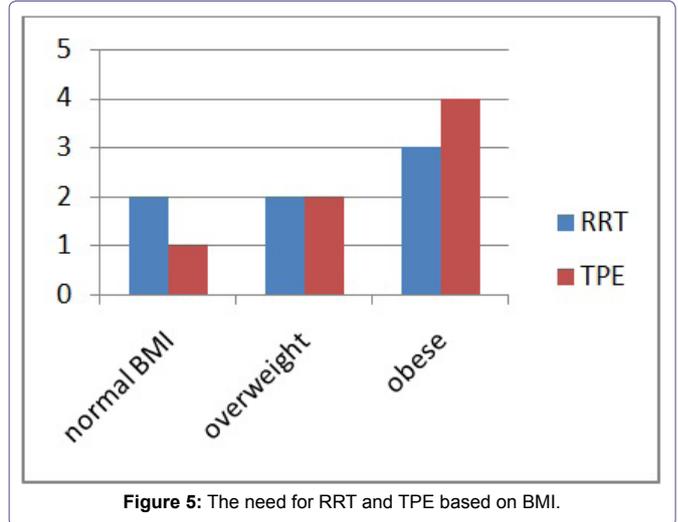


Figure 5: The need for RRT and TPE based on BMI.

Of the 9 patients with greater than 50% crescents on their biopsy 4 needed RRT, 4 needed TPE and 7 resided more than 10 miles away. A normal glomerulus (Figure 6a) is easily differentiated from one that has AAV involvement. Renal biopsies were performed on all 22 patients and showed different degrees of crescents and fibrosis (Figure 6b-e).

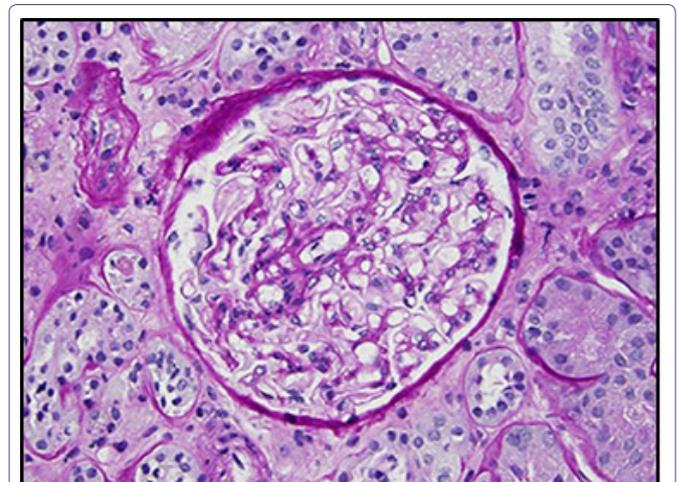


Figure 6a: Renal histology - a low power image of PAS stain showing a normal glomerulus in a 64 year old male patient.

Discussion

Microscopic Polyangitis (MPA), Granulomatosis with Polyangitis (GPA, formerly called Wegner's granulomatosis), Eosinophilic Granulomatosis with Polyangitis (EGPA, formerly Churg-Strauss

syndrome) and Renal Limited Vasculitis (RLV) or idiopathic Rapidly Progressive Glomerulonephritis (RPGN) syndromes are

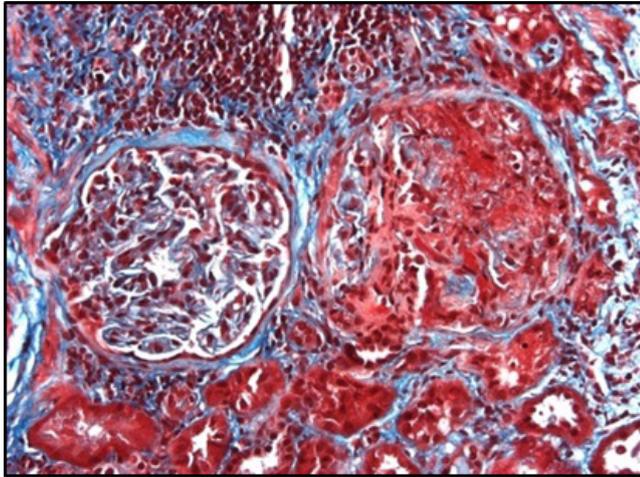


Figure 6b: Renal histology in a patient with AAV. A low power image of trichrome stain - two glomeruli, one on right with a crescent and fibrinoid necrosis.

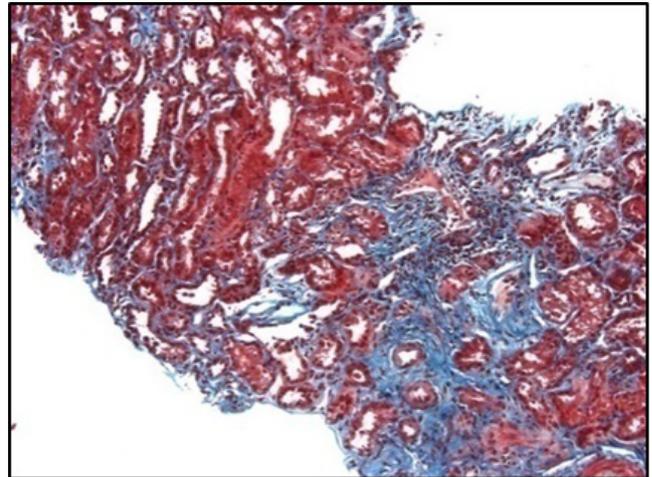


Figure 6e: Renal histology in a patient with AAV. A low power image of trichrome stain showing significant fibrosis.

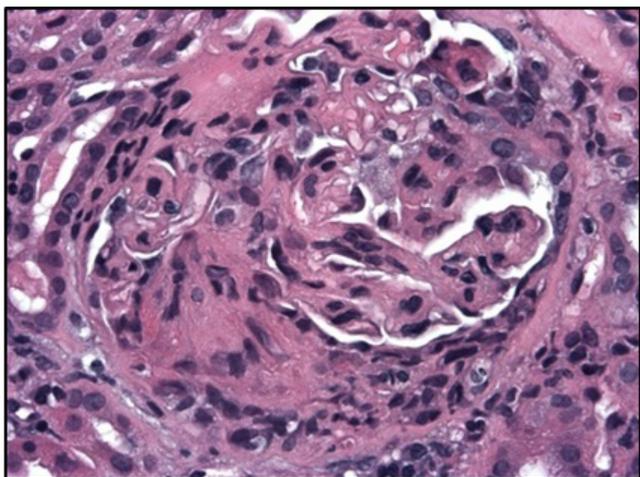


Figure 6c: Renal histology in a patient with AAV. A high power image of H&E stain showing a cellular crescent.

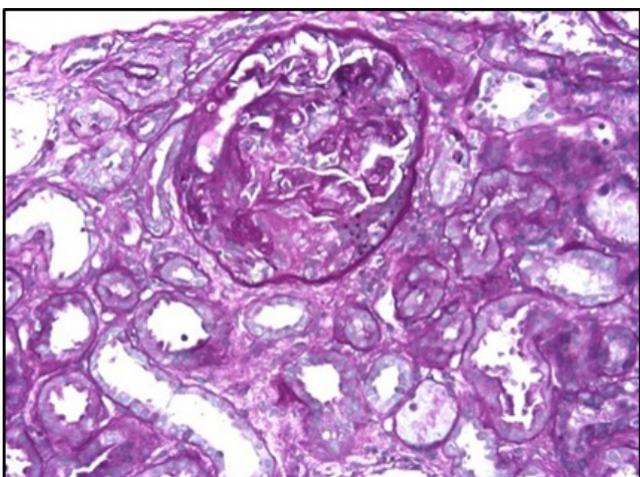


Figure 6d: Renal histology in a patient with AAV. A low power image of PAS stain showing a crescent.

characterized by the presence of necrotizing lesions of small vessels and the regular presence of antibodies against cytoplasmic antigens in

neutrophils ANCA and therefore are grouped together as ANCA Associated Vasculitis (AAV) [1]. Anti-Neutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitides (AAV) is a group of small vessel vasculitides that are described as being pauci-immune.

Two major categories of ANCA can be recognized by Indirect Immunofluorescence microscopy (IIF) on ethanol-fixed neutrophils: a Cytoplasmic (C-ANCA) and a Perinuclear (P-ANCA) staining pattern [9-11]. Sera that produce the C-ANCA pattern nearly always react with Proteinase 3 (PR3) [12,13]. The major P-ANCA target is Myeloperoxidase (MPO), but antibodies against other neutrophil antigens, such as elastase, lactoferrin and cathepsin G, and even antinuclear antibodies can produce a similar staining pattern [14-17]. Antibodies against PR3 are predominantly found in patients with active Wegener's granulomatosis and microscopic polyangitis [18]. Antibodies against MPO are also found in patients with microscopic polyangitis as well as in patients with Churg-Strauss syndrome, idiopathic necrotizing crescentic glomerulonephritis, and drug induced vasculitis [18].

AAV occurs more frequently in Caucasians than in people with African American descent, with the incidence being slightly greater in males than in females [19,20]. The population of the United States is aging. It is anticipated that the population of Americans aged 65 years or older will double during the next 25 years to about 72 million [21]. Although ANCA-Associated Vasculitis (AAV) is rare in the general population, epidemiologic data demonstrates that it has a predilection for older individuals with some studies citing a peak incidence in the 65-74 year age group [22,23]. As per the West Virginia data the obesity rate is highest at 40.2% in the 45-64 year age group and affects 34.7% whites. Analysis from our series shows that 100% of the population was Caucasian with 50% of the affected patients being males. Overall only 6 patients (27.3%) were elderly. Our results did show a predominantly overweight or obese population as 11 patients (50%) was overweight and 6 patients (27.3%) were obese. Is this high rate due to the patient population of this area with the second highest obesity rate in the country or are obese and overweight patients more likely to have AAV is unclear and needs further exploration.

Treatment of AAV is based on the stage of the disease and its severity. Many studies including the one by Franssen et al., [18] have shown a large divergence in the disease spectrum between patients with anti-PR3 and those with anti-MPO. Studies have shown that,

irrespective of the specific diagnosis, extrarenal organ manifestations and respiratory tract granulomas are more frequent in patients with PR3-AAV than in patients with MPO-AAV [18,24]. Patients with necrotizing crescentic glomerulonephritis and PR3-AAV have a more dramatic deterioration of renal function compared with patients who have MPO-AAV. However, renal survival is significantly worse in patient with MPO-AAV than in those with PR3-AAV [25]. This study also showed that the relapse rate in patients with PR3-AAV was far higher than in patients with MPO-AAV, irrespective of the treatment group [26,27]. The prevalence of renal involvement does not differ between anti-PR3 and anti-MPO positive patients with vasculitis and is approximately 75 to 90% [18,28,29]. Several studies have shown that the renal lesions associated with anti-PR3 and anti-MPO are essentially the same [30,31]. Several studies have shown that upper respiratory tract involvement is more frequent in anti-PR3 than in anti-MPO positive patients with necrotizing crescentic glomerulonephritis [18,29,32]. Pulmonary cavitating lesions are more frequently present in anti-PR3 patients [32]. Ter Maaten et al., found that acute respiratory failure caused by alveolar hemorrhage occurred more frequently in anti-PR3 than anti-MPO positive patients with vasculitis, suggesting a more severe course in anti-PR3 positive patients [33]. Few studies have reported a preponderance of males in patients with anti-PR3 and of females in patients with anti-MPO associated vasculitis [28,32].

The relation between PR3 or MPO positivity and BMI has not been reported thus far. Our results suggested a high prevalence of being either overweight or obese in patients with PR3 as compared to MPO. The physiological basis to the association between AAV with being overweight and obese is not really known to date. Visceral adipose tissue is an active endocrine organ and a source of pro-inflammatory cytokines as well as adipokines [34]. However one may hypothesize that perhaps just like how Petermann Smits et al., recently reported an increased prevalence of metabolic syndrome in patients with AAV and how it may have an impact on the clinical course of AAV and correlation with elevated CRP levels [35]; obesity or the presence of increased leptin levels may play a role in pre-disposing patients to AAV and place them at a higher risk for more severe disease. Activation of the immune system in AAV is thought to increase the risk of acceleration of atherosclerosis and increase risk for cardiovascular events in patients with metabolic syndrome [36]. Thus it may be postulated that the presence of increased visceral adipose tissue may be responsible for making this population vulnerable to AAV.

Hauer et al., [37] in their study concluded that glomerulonephritis due to microscopic polyangiitis has more characteristics of chronic injury at the time of presentation than glomerulonephritis in relation to Wegener's granulomatosis. This difference could be due to the delay in diagnosis in patient with MPA compared to patients with GPA. Distance from the biopsy site seems to play an important role in the extent of injury noted at presentation and the severity of the disease in terms of the need for RRT or TPE. We found that 15 patients (68.2%) resided more than 10 miles from the biopsy center and of these 7 patients (46.7%) had more than 50% crescents on their biopsy, 3 patients (20%) needed RRT while 4 patients (26.7%) needed TPE for the treatment of their AAV. This suggests that distance from the biopsy center does have some relation to the degree of injury and severity of disease as increasing distance delays diagnosis and leads to more progression of the disease and severe presentation that then warrants RRT or TPE for treatment of the AAV.

Treatment of AAV can be divided into three phases, initial induction immunosuppression, maintenance immunosuppression and treatment of relapses. Induction usually involves treatment with corticosteroids and cyclophosphamide. A subset of patients will end up needing RRT that is dialysis for their acute kidney injury; meanwhile a subset may also require therapeutic plasma exchange as part of their treatment regimen. Plasma exchange may be of benefit in three specific conditions: (i) life threatening pulmonary hemorrhage, (ii) dialysis dependent renal failure at the time of presentation with a serum creatinine > 5.6mg/dL or (iii) concurrent anti-Glomerular Basement Membrane (GBM) antibody disease [30]. Based on Jayne et al., study plasma exchange was associated with a 24% reduction of the risk of progression to end stage renal disease [38]. The MEPEX trial also showed that plasma exchange compared with pulse methylprednisolone increases the rate of recovery from renal failure. Several studies have found that renal function over time is worse when patients are already dialysis dependent at diagnosis [39-41]. In our series 7 patients (31.8%) needed RRT and 7 patients (31.8%) needed TPE due to severity of their disease. Of these patients who needed RRT and TPE a significant proportion were either obese or overweight. Thus one may hypothesize that just like obesity increases risk for acute kidney injury; being overweight or obese may increase the likelihood that if AAV is to occur the presentation may be severe enough to warrant RRT or TPE.

The gold standard for a diagnosis of AAV is histologic evidence of small vessel vasculitis in the context of a clinical constellation with respiratory and renal symptoms together with a positive ANCA result [42]. The prognosis for AAV has changed dramatically during the last 50 years, most notable for GPA. In the 1950s the mean survival of untreated WG was 5 months with less than 10% surviving 2 years [43]. After the introduction of cyclophosphamide and corticosteroids as standard treatment, patients now experience a one year survival of 93% and a 5 year and 10 year survival of 79% and 75% respectively [44]. Histologically, the characteristic glomerular lesions of acute pauci-immune ANCA glomerulonephritis are crescents and fibrinoid necrosis. The glomerular lesions may be accompanied by necrotizing arteritis. Interstitial edema is commonly seen with severe acute pauci-immune ANCA glomerulonephritis [4]. Analysis from the EUVAS group showed that the age, renal function at the time of diagnosis, normal glomeruli percentage, and tubulointerstitial lesions were predictors of GFR at 12 months. Dialysis dependency was predicted by the percentage of fibrous crescents at entry, percentage of normal glomeruli and treatment arm [45]. Robert et al., [46] study showed that in patients with dialysis-dependent, ANCA associated vasculitis, the chances of recovery differ depending on the type of adjunctive treatment, the percentage of normal glomeruli and glomerulosclerosis, the extent of tubular atrophy, and the presence of arteriosclerosis. The results from our series reflected that those who presented with more than 50% crescents on renal biopsy 44.4% needed RRT and TPE and hence accounted for increased severity of the disease.

We acknowledge several limitations of this study, first and for most is the small sample size. It is important to realize that this is a retrospective case series report. Potentially having a larger sample size may make the results of our study statistically significant. Secondly our cases were predominantly Caucasian. By virtue of the single-center study design, the results may not be generalizable to other settings. The fact that the study center was located in West Virginia which is ranked as number two in terms of the state with the

highest obesity rate in the United States, there could potentially have had some degree of effect on our study results. Other potential limitations are that it was a retrospective review of cases.

The need for renal replacement therapy for severe renal dysfunction in AAV is associated with poor survival and increased risk for progression to end stage renal disease [47]. The combination of older age and severe renal involvement from AAV portends a particularly grim outcome [41,48]. Histologic classification of glomerulonephritis in AAV has emerged as a potential predictor of long term renal outcomes [49]. In summary, we presented a case series of 22 patients with biopsy proven AAV. Our results did reflect a high prevalence of being overweight or obese as well as increased severity of illness at presentation as marked by the need for RRT and TPE. Also one may infer that the increased distance from the biopsy center increased the likelihood of more chronic injury to be found on the renal biopsy and an overall increased severity of illness at initial presentation warranting the need for RRT and TPE. Thus patients BMI and distance from the biopsy center should be considered when speculating the degree of severity of disease in a patient presenting with AAV. Further studies are required to determine definitely if increased BMI is indeed a risk factor for the development of AAV.

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