ANCA-Associated Vasculitis with Cardiac Valve Vegetations in Two Teenage Males: A Case Report and Literature Review

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Case Report

Keywords: Valvular involvement, Granulomatosis with Polyangiitis, Pediatrics, Adolescent, ANCA-associated Vasculitis

Posted Date: January 12th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1178656/v1>

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Abstract

Background: Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis is a term used to describe systemic vasculitides that affect small and medium-sized blood vessels. The three types of ANCA-associated vasculitis (AAV) are Granulomatosis with Polyangiitis (GPA), formerly Wegener's granulomatosis, Microscopic Polyangiitis (MPA), and Eosinophilic Granulomatosis with Polyangiitis (EGPA), formerly Churg-Strauss, with clinical presentation most frequently involving the respiratory tract, the kidney, the skin and the joints. ANCA-associated vasculitis is rare in children, with estimated prevalence of 3-4 per million, and even more rare is the manifestation of cardiac abnormalities secondary to ANCA-associated vasculitis in the pediatric population.

Case Presentation: We present the cases of two teenage males who presented with cardiac valvular lesions secondary to Granulomatosis with Polyangiitis in addition to sinus, pulmonary, renal, and cutaneous involvement. These findings of cardiac valvular abnormalities in GPA have rarely been described in the literature in pediatrics. Both patients were treated with rituximab, high-dose methylprednisolone, and plasma exchange (PLEX) and showed improvement in their disease manifestations.

Conclusions: A review of the literature revealed only five pediatric cases of ANCA-associated vasculitis with cardiac manifestations, and interestingly, three of the five had valvular involvement. Subsequent valvular involvement makes obtaining the diagnosis of ANCA-Associated Vasculitis very difficult due to concern for underlying infectious endocarditis and can lead to misdiagnosis given the rarity of cardiac involvement in ANCA-associated vasculitis. Routine echocardiogram is not always completed in newly diagnosed GPA, yet cardiac involvement can lead to severe consequences as was seen with our first patient in the form of thromboembolic stroke. We discuss the importance of keeping AAV on the differential when cardiac lesions are present as well as the importance of regular cardiac screening in newly diagnosed patients with AAV, as it is a major factor of cardiac morbidity and mortality in the adult population and can contribute substantially to management decisions.

Background

Granulomatosis with Polyangiitis (GPA) is a primary systemic vasculitis involving small and medium-sized blood vessels that is characterized by inflammation within the blood vessel walls, causing eventual tissue ischemia and necrosis (1, 2). It is extremely rare in childhood, but among the anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAVs) GPA has been recognized as the most common AAV present in pediatrics, followed by Microscopic Polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA) (2, 3). Cardiac involvement is a rare manifestation of GPA or MPA and is estimated to affect only 5% of pediatric cases (4, 5). When cardiac involvement is present, pericarditis and/or conduction abnormalities are the typical manifestations according to adult studies (6, 7).

The diagnosis of GPA is based on a combination of factors, including clinical features, serological markers, and characteristic findings on biopsy (specifically inflammation of predominantly small to medium arteries, capillaries or small veins, or pauci-immune glomerulonephritis). A pediatric-specific classification criteria by the EULAR/Pediatric Rheumatology International Trials Organization (PRINTO)/Pediatric Rheumatology European Society (PReS), a pediatric-specific adaptation of ACR criteria, was developed using pediatric data and includes the following: upper airway involvement, pulmonary involvement, renal involvement, granulomatous inflammation, laryngotracheobronchial stenosis, and ANCA positivity, with minimum three of the six criteria required for classification (8). See Table 1 for specifics regarding the criteria. These criteria have been shown to be highly sensitive for GPA in children, with approximately 93% sensitivity (8).

At disease onset, the most common features of GPA in children include constitutional symptoms such as fatigue, weight loss and fever (88%), followed by renal (83%), pulmonary (74%), ear, nose, and throat (ENT) (70%), musculoskeletal (65%), cutaneous (47%), ocular (43%), gastrointestinal tract (36%), and nervous system (20%) (9). Cardiac involvement is extremely rare in GPA in both adults and children; In fact, in the largest cohort of children with a diagnosis of GPA (ARChiVe Cohort, n=183), only 5% of children (n=10) had cardiovascular manifestations (9). These cardiac manifestations were primarily venous thromboses; other manifestations were not mentioned (9). Cardiac evaluation is not routinely completed in patients who are asymptomatic upon presentation. When cardiac involvement is found in cases of positive ANCA, the diagnosis of AAV becomes very difficult as ANCA-positive infective endocarditis (IE) has been well-described in the literature and has been reported to mimic the clinical manifestations of AAV, such as constitutional symptoms, skin purpura, glomerulonephritis, arthralgia and thromboembolic phenomenon (10–17).

Here, we present two cases of pediatric GPA with significant valvular involvement in the form of vegetations, as well as both pulmonary and renal involvement, who presented within one year of each other at our hospital. In one patient, these cardiac findings were asymptomatic and his valvular vegetations led to thromboembolic stroke. Cardiac valvular abnormalities have rarely been reported as a

primary manifestation of GPA in the pediatric literature; we compare cases of pediatric cardiac abnormalities reported in the literature, the importance of initial cardiac evaluation and regular routine cardiac monitoring in patients diagnosed with AAV, and the importance of keeping AAV in the diagnosis in the context of cardiac abnormalities with negative infectious workup.

Case Presentations

Case 1

A 16-year-old male presented to our pulmonary service with a 6-week history of bloody noses, hemoptysis, cough, fatigue, weight loss, fevers, and dark urine. Upon presentation, he had hypertension with blood pressure ranges 120 – 166 / 44 – 92, hemoglobinuria (large) with RBC >100/hpf, proteinuria (100 mg/dL) with Protein to Creatinine ratio of 2.07, ESR 59 mm/hr, CRP 12.9 mg/dL, and hemoglobin 7.3 GM/dL. He was intermittently febrile with Tmax 38.8 degrees Celsius. His creatinine ranged between 0.79-0.98 mg/dL throughout his hospital stay. Due to persistent coughing and history of hemoptysis, he underwent chest CT which showed widespread bilateral ill-defined ground-glass opacities along the bronchovascular bundles (Figure 1). Rheumatology, Nephrology, and Infectious Disease were consulted. His ANCA pattern was positive for C-ANCA pattern 1:640 with PR3 812 AU/mL; his ANA was 1:80, with normal C3 and C4 and negative RNP, Smith, double-stranded DNA, antiphospholipid (cardiolipin IgG and IgM, beta-2 glycoprotein IgG and IgM, DRVVT and stacLOT) and anti-glomerular basement membrane antibodies. He underwent a thorough infectious workup that included serum testing for Tuberculosis, Histoplasmosis (both urine and serum), *Coxiella burnetii*, *Bartonella henselae*, *Bartonella quintana* and HIV, all of which was negative. His COVID-19 respiratory swab was negative. A bronchioalveolar lavage was completed for further infectious workup which was negative for AFB cultures and stain, fungal cultures and stain, and bacterial culture and stain. On hospital day 3, he underwent renal biopsy due to persistent hypertension and elevated protein/creatinine ratio. Renal biopsy showed focal necrotizing and crescentic glomerulonephritis with pauci-immune pattern on immunofluorescence staining. During his renal biopsy, he was found to have Mobitz II heart block on telemetry, which ultimately lead to his cardiac evaluation and cardiology consultation. Of note, he had an EKG on admission that was normal. His echocardiogram obtained on hospital day 3 showed thickened aortic valve leaflets with perforation within the right coronary leaflet as well as 1-2 small areas concerning for vegetation on the aortic valve with mild aortic regurgitation, as well as thickening of the anterior leaflet of the mitral valve with Ejection Fraction 60% (Figure 2). He was asymptomatic without palpitations, chest pain, or chest tightness. On hospital day 3, after completion of his echocardiogram, he had an acute ischemic event which resulted in left facial droop and left-sided hemineglect with abnormal sensations on his left side; Magnetic Resonance Angiogram (MRA) scan of the head confirmed moderate-sized acute infarct involving the right insula, adjacent frontoparietal operculum and right parietal lobe with scattered foci of punctate infarcts bilaterally, suggesting thromboembolic phenomenon. Due to concern for bacterial endocarditis with newfound valvular lesions, blood cultures were drawn. One bottle out of four returned positive >24 hours after collection growing coagulase negative *Staphylococcus*, a common contaminant. He was ultimately treated with 5 days of plasmapheresis and Rituximab 1000mg at week 0 and week 2 per ANCA-Vasculitis protocol as well as methylprednisolone pulse (30 mg/kg x 3 days, max 1000mg) followed by high-dose oral glucocorticoids 2mg/kg/day (18). He was initiated on lisinopril 10mg daily by cardiology for both hypertension and improvement in heart muscle function. Due to inability to rule out bacterial endocarditis based on one positive blood culture and findings on echocardiogram of valvular vegetations, he was also treated with four weeks of Ceftriaxone. He clinically did well, and four months post-induction with Rituximab he was asymptomatic and displayed normalization of inflammatory markers (CRP <0.5 mg/dL, ESR 2 mm/hr). He had no persistent neurological or cognitive deficits. He currently is in maintenance therapy with Rituximab (18 months post-hospitalization) with baseline creatinine 0.93 mg/dL, resolution of proteinuria and hematuria, baseline DLCO 90%, and resolution of his aortic valve vegetation with stable mild-moderate aortic valve regurgitation with perforation.

Case 2

A 16-year-old male presented to the Intensive Care Unit (ICU) due to acute hypoxic respiratory failure thought to be secondary to bacterial versus viral pneumonia. He had a history of stiff, painful knees and elbows three weeks prior that had resolved with NSAID use. He presented to an outside hospital a week before presenting to our ICU due to cough, congestion, fevers, and myalgias. He was tested for COVID-19 which was negative, although his chest X-ray was concerning for multifocal pneumonia. He was given Azithromycin, but his symptoms did not improve. He saw his primary care physician who re-tested him for COVID-19 (negative) as well as performed Influenza A testing (positive). He was given Amoxicillin and Doxycycline for concern for overlying bacterial pneumonia, however he then developed weakness and severe shortness of breath. He presented to outside emergency department where he was found to be febrile to 38.0 degrees Celsius and tachycardic, with saturations of 65% while on room air. He had elevated white blood cell count to 18.5 k/cumm, hemoglobin 8.3 mg/dL, creatinine 1.21 mg/dL, BUN 31 mg/dL, PT 17.1 seconds with INR 1.41, D-dimer 4,224 ng/mL DDU, troponin 3.36 ng/mL, CRP 25 mg/dL, ESR 14 mm/hr. His urine was significant for large hemoglobinuria with 6-10 RBC/hpf. A repeat chest X-ray showed the development of large bilateral pneumothoraces with pneumomediastinum and dense opacities in both lungs. He required high-flow nasal

cannula but soon transitioned to Bilevel positive airway pressure (BiPAP) and ultimately intubation. He was then transferred to our center and placed on Venovenous (VV) extracorporeal membrane oxygenation (ECMO) due to severe respiratory failure secondary to pulmonary hemorrhage on day 2 of hospitalization; Bronchoalveolar lavage (BAL) completed on hospital day 2 was also consistent with pulmonary hemorrhage. An echocardiogram was completed on admission which showed a probable thrombus/vegetation on the mitral anterior leaflet near the septal attachment, trivial mitral regurgitation with normal tricuspid valve, and ejection fraction of 67%; Cardiology was immediately consulted. He was initiated on broad spectrum antibiotics (Cefepime, Gentamicin, Vancomycin) upon admission due to concern for overlying bacterial pneumonia and infectious endocarditis. Due to diffuse pulmonary hemorrhage, significant acute respiratory distress syndrome and requirement for VV ECMO, Pediatric ICU team began methylprednisolone 2mg/kg/day from day 2 – day 4 of hospitalization. Of note, while on 2mg/kg/day of methylprednisolone his creatinine improved from 1.21 mg/dL to 0.86 mg/dL, and then rose slowly after discontinuation of IV methylprednisolone; his VV ECMO settings were also able to be decreased while receiving methylprednisolone, with slow worsening of lung function after discontinuation. Rheumatology, Nephrology, and Infectious Disease were consulted on day 9, day 12, and day 6 of hospitalization respectively.

A thorough infectious workup ensued on day 6 of hospitalization. Serologies for Hepatitis A, B, and C, Bartonella henselae, Bartonella quintana, and HSV were sent and were negative. Multiple blood culture samples were sent throughout his hospital stay and were negative. PCR respiratory viral swabs for Parainfluenza, RSV, Bordetella parapertussis, Bordetella pertussis, Chlamydia pneumoniae, Mycoplasma pneumoniae, COVID-19, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Influenza A and Influenza B were negative. BAL studies including AFB stain and culture, fungal stain and culture, bacterial stain and culture, and universal PCR were unremarkable. Of note, Aspergillus antigen in his BAL sample was slightly positive, with antigen Index in BAL 0.55 (normal <0.5), though our infectious disease team did not feel this was a true positive. His ASO and DNase B were negative. On hospital day 6 a chest CT-Angiogram was completed to evaluate the extent of thromboembolic phenomenon given cardiac vegetations, which showed diffuse consolidation of both lungs without evidence of pulmonary arterial embolic disease, with consolidation likely representing a combination of atelectasis and edema although a component of hemorrhage or infection also possible. On hospital day 6, he developed splinter hemorrhages on examination, followed by scattered petechiae on hospital day 7 consistent with leukocytoclastic vasculitis confirmed by skin biopsy. Repeat echocardiogram on hospital day 8 re-demonstrated small mitral valve vegetation as well as likely perforation of the anterior leaflet near the medial annulus (Figure 2). Rheumatology was consulted on day 9 of hospitalization due to worsening hematuria (RBC on admission 6-10/hpf, hospital day 9 with RBC now >100/hpf) with large hemoglobinuria and worsening protein/creatinine ratio (now 3.72), pulmonary hemorrhage, leukocytoclastic vasculitis, overall negative infectious workup, and vegetations on echocardiogram with concern for an underlying rheumatologic disorder.

Rheumatologic evaluation showed normal C3 and C4, negative Double-Stranded DNA, anti-Smith/RNP, SSA, SSB, anti-Cardiolipin IgM and IgG, beta-2 glycoprotein IgM and IgG, anti-GBM, and ANA. His ANCA panel was sent on hospital day 9 and returned on hospital day 14 consistent with c-ANCA pattern 1:5120 with PR3 1542 AU/mL. By this time, his renal function had deteriorated to the point where he developed hyperkalemia and required continuous venovenous hemofiltration (CVVH) initiated on hospital day 11. He remained on VV ECMO which made obtaining a renal biopsy extremely dangerous due to risk of bleeding. On hospital day 11, given rapidly progressing rash, worsening renal function and hyperkalemia requiring CVVH, negative infectious workup thus far, pulmonary hemorrhage and inability to obtain biopsy given VV ECMO, he initiated pulse methylprednisolone 500mg q12 for a total of 3 grams. He also began a five-day course of plasmapheresis. Upon initiation of pulse methylprednisolone and plasmapheresis, his lung function and kidney function improved; he was decannulated from VV ECMO on hospital day 20 and discontinued CVVH on hospital day 19. A renal biopsy was obtained on hospital day 22 which was significant for segmental fibrinoid necrosis without crescent formation and pauci-immune pattern on immunofluorescence, further supporting the diagnosis of Granulomatosis with Polyangiitis. When stabilized, he underwent a CT scan of his chest which showed diffuse symmetric ground glass opacities bilaterally as well as two well-defined solid appearing soft tissue density nodules in the right middle lobe and another nodule in the upper aspect of the major fissure of the left lung (Figure 2).

For Granulomatosis with Polyangiitis, he received high-dose pulse glucocorticoid for 3 days (hospital day 11-13) followed by high-dose oral glucocorticoids (prednisone 30mg twice daily), plasmapheresis for 5 consecutive days (hospital day 11-15), and ultimately Rituximab 375 mg/m² every week (first dose on hospital day 30) for a total of four doses per protocol followed by 1000mg every 6 months (18). Due to inability to completely rule out infectious endocarditis despite negative blood cultures, he also completed 4 weeks of IV Ceftriaxone therapy. He did initiate treatment for Aspergillus due to positive Aspergillus antigen in BAL and known need for immunosuppression with B-cell depleting therapy. Due to persistent hypertension, proteinuria, and risk of cardiac remodeling, he was initiated on lisinopril 10mg daily per cardiology and nephrology recommendations. He is now 10 months post-hospitalization and is in maintenance therapy with Rituximab 1000mg every 6 months, with baseline creatinine around 1.5 mg/dL and resolution of hematuria and proteinuria, improved lung function with most recent DLCO at 74% (lowest value prior to discharge from the hospital 42%), and resolution of mitral valve vegetation with stable mild mitral regurgitation with persistent perforation within the anterior mitral valve leaflet.

Discussion

The two cases above highlight significant valvular involvement in granulomatosis with polyangiitis in two teenage male patients, an extremely uncommon finding in the pediatric literature. Based on our literature search, only five patients within the pediatric age realm have been described as having cardiac involvement (Table 2). Interestingly, three of the five had cardiac valvular abnormalities, possibly suggesting valvular abnormalities, while still rare, may be more prevalent in the pediatric age group when present. In adults, the most prominent valve abnormalities seen in one study in patients with EGPA and GPA was the aortic valve in the form of aortic regurgitation (19). The ARCHiVe cohort, the largest cohorts of pediatric patients diagnosed with GPA described in the literature, found no cardiovascular manifestations at presentation out of 65 patients (4); A follow up study demonstrated only 10 patients out of 183 with cardiovascular manifestations (9), and a separate cohort described zero patients out of 38 (5). These cohorts highlight the rarity of cardiac manifestations in Granulomatosis with Polyangiitis.

For our first case, cardiac involvement was incidentally found due to the presentation of Mobitz type II heart block while undergoing renal biopsy and subsequent echocardiogram that was obtained due to this conduction abnormality. This patient was asymptomatic from a cardiac standpoint, yet ultimately developed thromboembolic stroke due to his cardiac involvement. To our knowledge this is the first case reported regarding cardiac valvular involvement leading to thromboembolic stroke in Granulomatosis with Polyangiitis. Thankfully our patient did not have lasting deficits. Patients with GPA have been asymptomatic yet still with cardiac involvement as evident by electrocardiogram and echocardiogram results, and cardiac involvement has been described as a strong predictor of cardiac mortality in adult studies (19). Given the high mortality and possible consequences (i.e., thromboembolic stroke) of cardiac involvement in patients with GPA, screening echocardiograms should be performed, as it may prove beneficial to not only gauge disease severity but also guide therapy and management decisions to prevent complications of this rare form of vasculitis.

The second case demonstrated cardiac involvement that was initially thought to be due to infectious endocarditis, however upon further evaluation it was found to be secondary to Granulomatosis with Polyangiitis. This case was extremely challenging given the severity of the patient's presentation and limitations to obtain tissue specimens to help with the diagnostic evaluation while on VV ECMO. ANCA antibodies, while strongly associated with systemic vasculitides, have also been described in other conditions and during various infections, including bacterial endocarditis, and patients with infective endocarditis have been described as having more severe renal manifestations (10–12). Our patient had persistently negative blood cultures throughout his hospital stay; In patients with ANCA-positive infective endocarditis, positive blood cultures are typically more prevalent than in ANCA-negative infective endocarditis (13, 17). Furthermore, our patient's renal function and lung function improved while on pulse-dose corticosteroids and did not improve while on antibiotic therapy alone, supporting an autoimmune cause for his presentation. B-cell depleting therapy was not initiated in our patient until a complete infectious workup had been completed and returned unremarkable and a renal biopsy had been obtained. His renal biopsy was supportive of the diagnosis of ANCA-Associated Vasculitis with segmental fibrinoid necrosis without crescent formation and pauci-immune pattern on immunofluorescence, though pauci-immune pattern has been described in patients with ANCA-positive infective endocarditis (14, 15). However, patients with ANCA-positive infective endocarditis typically have organ involvement limited to skin and kidneys, positive blood cultures, abnormal levels of complement, immune deposits, and other autoantibodies present (i.e., rheumatoid factor, antinuclear antibodies, anticardiolipin antibodies) (13, 15, 16, 18). Our patient did not have any of these additional findings and had additional lung involvement. This case highlights the diagnostic challenge in a patient with cardiac valvular vegetations, rash, fevers, pulmonary and renal involvement and positive ANCA; In such cases, it is imperative to rule out infectious etiologies and ideally attempt confirmation of the diagnosis with biopsy prior to initiation of immunosuppression, however this may not be always possible due to the severity of the clinical presentation and empiric treatment with antibiotics and immunosuppression might be required.

Conclusions

These two cases highlight cardiac involvement in granulomatosis with polyangiitis in two teenage males and the significant consequences that can occur from such involvement as well as the diagnostic dilemma that occurs secondary to such involvement. Cardiac valvular involvement is a rare manifestation of GPA in pediatrics, having only been reported in 5 cases (Table 2) (20–24). While cardiac involvement in adults has been associated with increased all-cause cardiac mortality, it is relatively unknown what the prognosis of cardiac involvement implies for children (19). Cardiac evaluation with echocardiogram is essential in pediatric cases of vasculitis to fully evaluate the extent of disease and to help guide treatment and management decisions. When cardiac involvement is found in cases of ANCA-positivity with multi-organ involvement, a thorough infectious workup should be completed, and biopsy should ideally be performed to both rule out an infectious process and further confirm the diagnosis of ANCA-associated vasculitis prior to initiation of immunosuppressive therapy.

Abbreviations

ANCA: anti-neutrophil cytoplasmic antibody

AAV: ANCA-Associated Vasculitis

GPA: Granulomatosis with Polyangiitis

MPA: Microscopic Polyangiitis

EGPA: Eosinophilic Granulomatosis with Polyangiitis

CVVH: Continuous Veno-Venous Hemofiltration

PR3: Proteinase 3

VV ECMO: Venovenous Extracorporeal Membrane Oxygenation

MPO: Myeloperoxidase

IV: Intravenous

IE: Infective Endocarditis

BAL: Bronchoalveolar lavage

MRA: Magnetic Resonance Angiogram

CT: Computerized tomography

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Obtained from patients and legal guardians

Availability of data and materials: Not applicable

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable

Authors' Contributions: AT conducted literature review, draft of manuscript, and preparation for publication. MR conducted edits to manuscript and preparation for publication.

Acknowledgements: Not applicable

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Tables

Table 1: EULAR/PRINTO/PReS Criteria for Childhood Granulomatosis with Polyangiitis

A patient is said to have GPA when three of the following six criteria are present:	
Upper Airway Involvement	Chronic purulent or bloody nasal discharge, or recurrent epistaxis/crusts/granulomata Nasal septal perforation or saddle-nose deformity Chronic or recurrent sinus inflammation
Pulmonary Involvement	Chest X-ray or CT scan showing the presence of nodules, cavities, or fixed infiltrates
Renal Involvement	Proteinuria >0.3g/24H, or greater than 30 umol/mg of urine albumin/creatinine ratio on a spot morning sample Hematuria or red blood cell casts: >5 red blood cells per high-power field, or red blood cell casts in urinary sediment, or >2+ on dipstick Necrotizing pauci-immune glomerulonephritis
Granulomatous Inflammation	Granulomatous inflammation within wall of artery or in perivascular or extravascular area of artery or arteriole
Laryngotracheobronchial stenosis	Subglottic, tracheal, or bronchial stenosis
ANCA	ANCA positivity by immunofluorescence or by ELISA (MPO/p or PR3/c ANCA)

ANCA, antineutrophil cytoplasmic antibody; CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; EULAR, European League Against Rheumatism; GPA, granulomatosis with polyangiitis; MPO, myeloperoxidase; PRINTO, Pediatric Rheumatology International Trials Organization; PR3, proteinase 3; PReS, Pediatric Rheumatology European Society

Table 2: Pediatric Cases of ANCA-Vasculitis Associated with Cardiac Involvement

Author	Patient Age, Sex	Onset of Cardiac Involvement	Description of Cardiac Involvement	Other organ involvement	ANCA-titer at time cardiac involvement found (pattern and antigen)	Treatment	Outcome
Harris et al. (20)	14yo, F	Diagnosis	Ovoid, homogenous pedunculated mass in apex of left ventricle with EF 40%	Upper and lower respiratory tract, cutaneous, arthritis, renal	C-ANCA (titer not available); PR3 148 EU/mL	Pulse glucocorticoids (30mg/kg) followed by methylprednisolone 2 mg/kg/day, cyclophosphamide 1 mg/kg/day, 7 days PLEX; mass resection	Unknown
Kosovsky et al. (21)	16yo, M	Diagnosis	Ventricular tachycardia, mass involving full thickness of right anterior ventricular wall extending into base of papillary muscles of the anterior leaflet of the tricuspid valve; biopsy revealed acute and organizing granulomatous vasculitis	Upper and Lower respiratory tract	ANCA studies negative	Cyclophosphamide (exact dosing not provided), Prednisone (exact dosing not provided)	Unknown
Varnier et al. (22)	16yo, M	Diagnosis	Vegetation adjacent to tricuspid valve	Cutaneous, upper and lower respiratory tract, renal, genital	C-ANCA (titer not available); PR3 194 EU/mL	Methylprednisolone pulse 1g daily for 3 consecutive days followed by high dose oral prednisolone; 10 days PLEX; Rituximab 1g at week 0 and 2; Cyclophosphamide 500 mg/m ² every 3 weeks for 4 doses	Normalization of renal function, resolution of inflammatory markers, recovery of symptoms; ultimately remission on treatment with prednisolone 3mg daily, Azathioprine 125mg daily, Amlodipine 5mg daily
Leff et al. (23)	17yo, M	Diagnosed 1 year after treatment	Mild LV enlargement, AI, AV perforation	Cutaneous, upper and lower respiratory tract, arthritis	C-ANCA 1:512; PR3 (exact unavailable)	Oral cyclophosphamide 150mg/day, prednisone 40mg/day	AV replacement due to progressive insufficiency; flare -> re-initiation of cyclophosphamide, oral prednisone, bactrim
Moghadam et al. (24)	10yo, M	Diagnosis	Diffuse ectasia and dilation with large aneurysm in the left anterior descending artery (14mm)	Perforated otitis media with effusion, saddle nose deformity, mastoiditis, sinusitis, deep vein thrombosis	P-ANCA (titer not available); antigen not provided	Methylprednisolone pulse (30 mg/kg/day for 3days/monthly), cyclophosphamide 750mg/m ² /monthly for 6 months. Oral prednisolone 1mg/kg/day, mycophenolate mofetil 1200 mg/m ² /day. Aspirin 5mg/kg, warfarin 0.1 mg/kg.	Maintenance therapy with low-dose prednisolone, mycophenolate mofetil, antithrombotic therapy. No flare 1.5 years after diagnosis.

Figures

Figure 1

Echocardiogram abnormalities for the two patients described above.

A., B.: Demonstration of Aortic Valve Vegetation for Patient 1.

C., D.: Demonstration of Mitral Valve Vegetation for Patient 2.

Figure 2

CT SCAN FINDINGS FOR PATIENT 1 AND 2 DESCRIBED ABOVE.

A., B., C.: CT chest of Patient 1. Final read: Ill-defined, confluent groundglass attenuation is present bilaterally in the lungs, roughly following the bronchovascular bundles. No dense consolidation is seen. No pleural effusions are identified.

D., E., F.: CT Chest of Patient 2. Final read: Subtle diffuse symmetric ground glass opacities throughout both lungs. Findings may represent pulmonary hemosiderosis related to sequela of prior diffuse bilateral pulmonary hemorrhage. Two well defined solid appearing soft tissue density nodules within the right middle lobe with surrounding tiny parenchymal cysts are present. Another similar appearing well defined nodule centered in the upper aspect of the major fissure of the left lung where it contacts the mediastinum is present. These nodular opacities are without cavitation or calcification and were not clearly seen on prior portable chest radiographs. Evaluation is limited due to the lack of IV contrast and their etiology is unclear. The tiny parenchymal cysts adjacent to the nodules in the right middle lobe could represent sequela of a necrotizing lung process. These nodules could represent organized parenchymal or pleural hematomas. The appearance is not highly suggestive of infection due to lack of surrounding inflammation. Neoplasm seems unlikely given the history.