

PULMONARY MICROSCOPIC POLYANGIITIS PRESENTING AS ACUTE RESPIRATORY FAILURE FROM DIFFUSE ALVEOLAR HEMORRHAGE

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ABSTRACT. Microscopic polyangiitis and granulomatosis with polyangiitis are rare anti-neutrophilic cytoplasmic antibody-associated systemic vasculitides that predominantly affect small to medium sized vessels of the lungs and kidneys. These syndromes are largely confined to older adults and often present sub-acutely following weeks to months of nonspecific prodromal symptoms. While both diseases often manifest within multiple organ systems concurrently, the disease spectrum of microscopic polyangiitis almost always includes the kidneys, while granulomatosis with polyangiitis is most commonly associated with pulmonary disease. We present two cases of rapid onset respiratory failure secondary to diffuse alveolar hemorrhage in young active duty military personnel. After serological testing and surgical lung biopsy, both patients were diagnosed with microscopic polyangiitis with isolated pulmonary involvement. (*Sarcoidosis Vasc Diffuse Lung Dis* 2015; 32: 372-377)

KEY WORDS: diffuse alveolar hemorrhage, microscopic polyangiitis, acute respiratory failure

Abbreviations

MPA	Microscopic polyangiitis
GPA	Granulomatosis with polyangiitis
AAV	ANCA associated vasculitis
ANCA	Anti-neutrophilic cytoplasmic antibody
FOB	Fiberoptic bronchoscopy
BAL	Bronchoalveolar lavage
DAH	Diffuse alveolar hemorrhage
MPO	Myeloperoxidase
PR3	Proteinase 3

INTRODUCTION

Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) are rare, idiopathic antineutrophilic cytoplasmic antibody (ANCA)-associated systemic vasculitides that predominantly affect small to medium sized vessels of the lungs and kidneys. ANCA-associated vasculitides (AAV) are exceedingly rare with an overall annual incidence of 10-20 cases per million in Europe and North America (1). They can occur at any age but are far more common in older adults with a peak onset between 65 and 74 years of age (1). As much as 70% of the time affected individuals present following weeks to months of prodromal constitutional complaints such as fever, myalgias, or arthralgias prior to initial diagnosis (2). Microscopic polyangiitis and GPA are closely related in their spectrum of disease and have comparable treatment regimens, but can vary

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widely in clinical course and most notably differ in their strong associations with specific ANCA. Microscopic polyangiitis is more commonly related to myeloperoxidase (MPO)-ANCA (30-80%) while GPA is more often associated with proteinase-3 (PR3)-ANCA (70-95%) (3). Both MPA and GPA can manifest within multiple organ systems and can cause cutaneous lesions, neuropathies, ocular symptoms, otolaryngeal abnormalities, and even disease of the gastrointestinal tract, in addition to the more common renal and pulmonary syndromes. Most often, the kidneys suffer the major burden of disease in MPA, while GPA primarily targets the lungs and head and neck (4). A recent review estimates that 80-100% of patients with MPA experience renal disease which can range from asymptomatic proteinuria to overt renal failure as related to the pauci-immune glomerulonephritis typically seen in AAV (5). Pulmonary disease, though not as predominant, has been reported in 22%-55% of patients (5, 6). The classic pulmonary manifestation is diffuse alveolar hemorrhage, reported in 11-36% of patients (2, 7). Granulomatosis with polyangiitis has a different distribution of disease with more than 90% of patients with GPA eventually developing upper airway or ear abnormalities (8), as many as 85% of patients with lung nodules or infiltrates (3), and fewer with renal disease.

Most patients with AAVs present following weeks to months of prodromal symptoms, and it is atypical for a patient to present with acute respiratory failure as an initial manifestation of the disease. Specifically with MPA, there are few case reports describing acute respiratory failure as the presenting symptom (9, 10). Furthermore, there are only a limited set of MPA case reports of isolated pulmonary disease, and fewer cases of acute respiratory failure from isolated diffuse alveolar hemorrhage (10, 11). The reports below portray two such unusual cases of acute respiratory failure in young military personnel found to be secondary to DAH resulting from MPA. These cases also share the unique feature of MPA involvement limited solely to the lungs.

CASE REPORT 1

A previously healthy 18 year old male Air Force basic trainee presented to an urgent care clinic with

three days of upper respiratory symptoms. He was febrile to 101.5°F, tachycardic at 113 beats per minute with normal respiratory rate and oxygen saturations. His examination was only notable for bilateral tonsillar erythema and exudates. He was treated with a course of oral azithromycin and ibuprofen for presumed tonsillitis. His symptoms continued unabated through the following day then he began to have intermittent hemoptysis and epistaxis. Repeat examination revealed decreased oxygen saturations to 92% with bilateral wheezing on pulmonary auscultation. Initial chest radiograph displayed diffuse patchy bilateral mixed interstitial and airspace opacification. He was immediately transferred to our tertiary care hospital where temperature was 98.5°F, blood pressure 91/55 mm Hg, heart rate 114 beats per minute, and oxygen saturation 96% on room air. He was initially well oriented and conversational, but over the next few hours his condition precipitously declined, and he became hypoxic with 70% oxygen saturations and altered mental status. The patient was urgently intubated for hypoxemic respiratory failure and repeat chest radiograph revealed strikingly worsened mixed airspace and interstitial opacities with confluent disease within the left mid lung and bilateral bases. Computed tomography of the chest displayed diffuse patchy airspace opacities with small low density bilateral lower lobe pleural effusions (Figure 1). Broad spectrum antibiotics and antiviral medications for presumed acute respiratory distress syndrome secondary due to a complicated multilobar pneumonia were initiated. Despite this treatment, the patient showed no clinical improvement and his ventilator settings remained unchanged for the first 24 hours. Fiberoptic bronchoscopy (FOB) was performed on hospital day #2 to obtain bronchoalveolar lavage (BAL) samples to isolate a possible infectious source. The initial BAL return was sanguineous and repeat aliquots confirmed DAH in the sampled lobe. Repeat FOB on hospital day #3 in different segments bilaterally revealed increasingly sanguineous lavage fluid aliquots again diagnostic for DAH. No organisms were isolated on BAL fluid cytology or cultures and all other cultures were negative.

Given the lack of infectious etiologies and a high suspicion for an autoimmune vasculitis, daily pulse methylprednisolone was initiated with rapid clinical and radiographic improvement (Figure 1). He was rapidly weaned from mechanical ventilation after

three days of pulse steroids. Renal evaluation demonstrated normal renal function and urinalysis. An extensive serological workup revealed the presence of PR3-ANCA (50 U/ml) in excess of MPO-ANCA (7 U/ml) which would rise to as high as >300U/ml and 48 U/ml respectively within the first week of diagnosis. Other rheumatologic markers such as anti-glomerular basement membrane, rheumatoid factor, anti-double stranded DNA, and anti-nuclear antibody were negative and complement levels were within normal limits. Surgical lung biopsy on hospital day #10 revealed a cellular interstitial pneumonia suggestive of acute lung injury with no evidence of granuloma formation. The patient was treated with six cycles of plasmapheresis followed by four cycles of rituximab therapy and an oral steroid taper with no clinical recurrence. ANCA levels dropped as expected following appropriate medical therapy to a PR3-ANCA of 68 U/ml and MPO-ANCA of 3 U/ml. Although, there was no evidence of vasculitis on

biopsy, after thorough evaluation by multiple subspecialists; to include dermatology, otolaryngology, pulmonary, and rheumatology, given the patient's elevated ANCA levels, lack of physical exam findings of GPA, and rapid clinical improvement with use of steroids and Rituximab, it was agreed that a diagnosis of MPA was most accurate in this case. Lung biopsy was not obtained until the patient had completed six days of methylprednisolone and two cycles of plasmapheresis resulting in rapid clinical stability.

CASE REPORT 2

A healthy, 22 year old Army female was deployed to Afghanistan for several months when she developed dyspnea on exertion with associated cough and scant hemoptysis. She was evaluated at a troop medical clinic and treated for an upper respiratory infection with a five day course of oral azithromycin. Over the next two weeks, her dyspnea continued to worsen and her cough progressed to frank hemoptysis. She again was evaluated at the troop medical clinic where she was placed on levofloxacin for empiric treatment of a presumed community-acquired pneumonia. Over the next five days, her symptoms progressed and she suffered a syncopal event in her barracks. Initial oxygen saturations were noted to be in the low 80s and her hemoglobin was measured at 6.0 gm/dL. After resuscitation with intravenous fluid and packed red blood cell transfusion, oxygen saturations were initially maintained with 100% oxygen to evacuate the patient to a higher level care at Bagram Air Force Base hospital.

Computed tomography of the chest revealed diffuse bilateral alveolar filling with ground glass attenuation (Figure 2), and she was subsequently intubated for hypoxic respiratory failure. She was medically evacuated from Afghanistan to Landstuhl Regional Medical Center, Germany for subspecialty care. Fiberoptic bronchoscopy was performed and consistent with DAH based on progressively bloody lavage aliquots and the presence of hemosiderin-laden macrophages. She was immediately started on pulse dose steroids for DAH, with a presumed etiology of acute eosinophilic pneumonia (given extensive clinical experience from Iraq and Afghanistan(12)), and extensive rheumatologic workup was initiated. Rapid improvement was noted on steroid

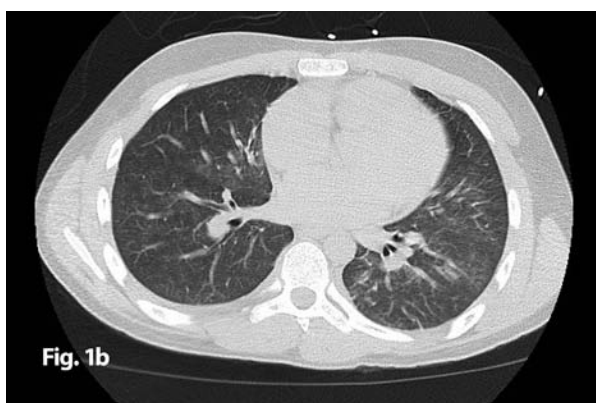
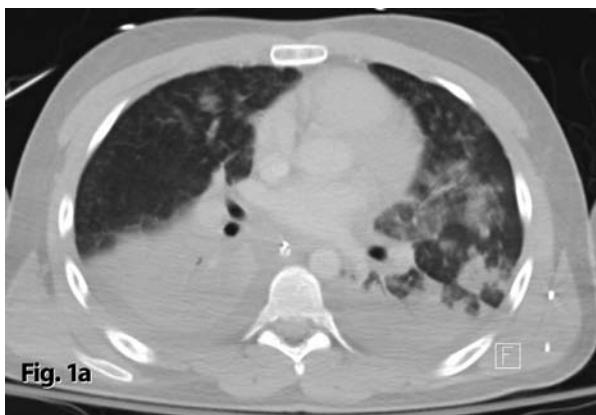


Fig. 1. Case 1 patient CT scan on HD#1 (a) and HD#10 (b) after 6 days of steroid therapy and 2 cycles of plasmapheresis

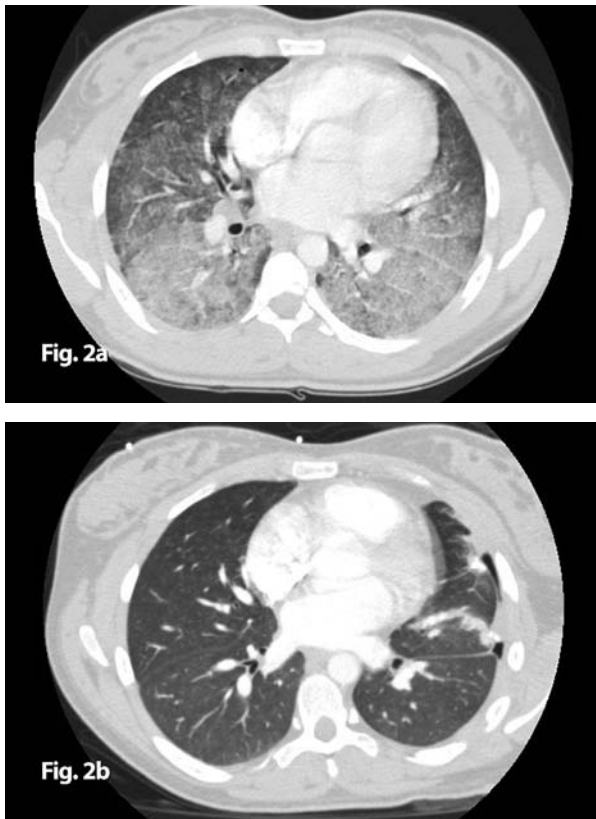


Fig. 2. Case 2 patient CT scan on initial presentation (a) and after recovery (b)

therapy and she was extubated without complication with subsequent final evacuation to San Antonio Military Medical Center. Laboratory evaluation demonstrated normal renal function with a normal urinalysis. Initial serologies returned MPO positive (134 U/ml) and PR3 negative (10 U/ml) and normal complement levels. Other negative serologies included anti-nuclear antibody, anti-phospholipid antibody, cyclic citrullinated antibody, anti-Smith nuclear antibody, glomerular basement membrane antibody, and systemic sclerosis antibodies. Surgical lung biopsy followed which revealed perivascular inflammation with alveolitis and capillaritis (Figure 3). Despite the lack of renal disease, her clinical picture of DAH in conjunction with a positive MPO-ANCA, histological evidence of vasculitis without granulomas, and otherwise negative serologic evaluation was most suggestive of MPA. She was initially placed on a prolonged prednisone taper for an estimated six to nine months. Several weeks later, her post-operative course was complicated by recurrent

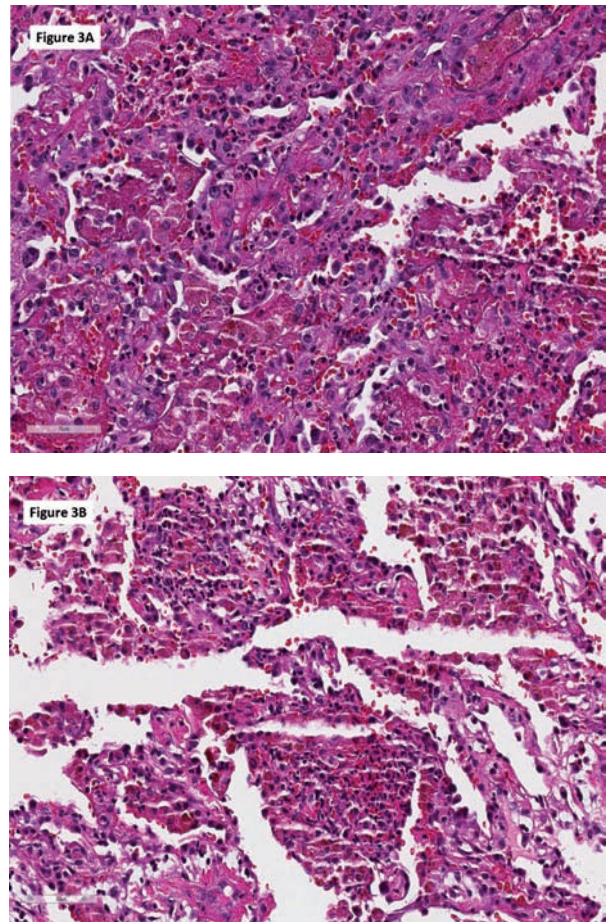


Fig. 3. (A) Microscopic Polyangiitis involving the lung with diffuse alveolar hemorrhage, alveolitis, and capillaritis. (B) Neutrophils and fibrin plugs within alveoli can mimic an organizing pneumonia

pneumothoraces requiring prolonged chest tube thoracostomy and subsequent left upper lobe wedge resection and mechanical pleurodesis. After resolution of the pneumothorax, she successfully completed a six month course with rituximab. The patient currently is doing well with no evidence of renal disease or recurrence of pulmonary symptoms.

DISCUSSION

The above cases illustrate two unusual initial presentations of MPA given these patients were relatively young, the pulmonary vasculature was the only system affected, and both presented acutely with potentially life threatening respiratory failure secondary to DAH. Microscopic polyangiitis is a necrotizing

systemic vasculitis of small to medium sized vessels that can result in a wide spectrum of organ involvement, but predominantly affects the kidneys (80-100%) more so than the lungs (22-55%). Patients generally present beyond their 4th decade of life, and onset of symptoms is most often insidious in nature, with the rare patient presenting acutely, particularly with acute respiratory failure.

Our two patients (18 year old male and 22 year old female) were exceptionally young to be presenting with this disease. Vasculitides are rare in youth and younger adults in general, but particularly so with regards to small vessel vasculitides. There are few case reports of MPA discovered in adults under 40 years of age (9, 10, 13-15). Little is known about MPA in young adults and there appears to be little analysis written on the matter. Examination of the reported cases suggests that females predominant over males in this age range and they appear to reach a fuller and faster recovery than older age groups. The incidence of pediatric GPA and MPA is small or unknown with some estimating 1 case per 2 million in the case of GPA and even less so with MPA (16). Most information on childhood/youth AAV are derived from case reports and most aspects of care are extrapolated from data about adults (17). A review by Arukuluman et al. (16) assessed seven reports describing the clinical course of 86 patients with pediatric onset AAV. In these patients disease onset ranged anywhere from two weeks to 16 years with a female predominance of 68% and 70% in GPA and MPA respectively. In this study and others, renal involvement appears to be the predominant feature of MPA in children, specifically with necrotizing glomerulonephritis occurring frequently in this cohort (18). Children and adolescents in general also tend to present similarly to adults with several weeks to months of insidious prodromal symptoms. Unlike adults, there appears to be a female predominance with AAV, as well as a seasonal variation, with more children/young adults presenting in the winter and spring months (19).

Isolated pulmonary involvement in MPA is exceedingly rare and difficult to confirm as vasculitides are often dynamic in character. Bosch et al describe several of the few previous reports of isolated pulmonary involvement in DAH (10, 11, 20). This same group would later illustrate the emergence of GPA in patients who previously by definition only

met criteria for MPA (21). This leads some to question the utility of the specific nomenclature for AAV, especially since the treatment regimens are virtually identical and further classification may be misleading to both physician and patient. Some have suggested a limited form of MPA in the form of interstitial lung disease as supported by multiple cases of isolated idiopathic pulmonary fibrosis predating other MPA manifestations for up to ten years (7, 22). Overall, there are an extremely limited number of reports of isolated pulmonary disease in MPA. However, given the young age of these patients, we cannot fully conclude that they will not develop extrathoracic involvement in the future.

Diffuse alveolar hemorrhage due to alveolar capillaritis is the most frequent lung manifestation of MPA for all ages, with some sources reporting occurrence in up to 36% of patients. However, with few exceptions; acute respiratory failure is almost never the initial manifestation of MPA. A study aiming to describe the pulmonary manifestations of MPA illustrated 29 cases of DAH. Of these cases, 69% had severe dyspnea but only 10% required treatment with mechanical ventilation (13). All of these patients had other systemic manifestations and it is unclear if pulmonary hemorrhage was the major contributor in each patient's morbidity or was present on initial diagnosis. There are two unique cases of acute respiratory failure from diffuse alveolar hemorrhage described by Bosch et al. (10) Both presented with less than two weeks of symptoms and required immediate mechanical ventilation. Another case describes a 25 year old pregnant female at 24 weeks gestation who presented with acute respiratory decline after just one week of symptoms (15). Similar to our cases, these patients appeared to recover quickly after an appropriate treatment regimen was initiated.

The third AAV is Churg-Strauss Syndrome which is now called eosinophilic granulomatosis with polyangiitis (EGPA). This is a disorder that appears to lie within the intersection of systemic ANCA vasculitides and hypereosinophilic syndrome. This syndrome is ANCA positive in approximately 30-40% of cases and is more often associated with glomerulonephritis (23). Rarely, EGPA has been associated with DAH (24, 25), but in only up to four percent of cases. Both of our patients had no history of asthma and lacked evidence of eosinophilia, thus, making EGPA extremely unlikely in these cases.

Finally, both patients were given Azithromycin at some point in the beginning of their illnesses. There has been at least one case report of azithromycin-induced DAH reported in the literature (26). However, azithromycin-induced DAH is unlikely in these patients given that their clinical, laboratory, and pathological findings and subsequent successful treatment with Rituximab, was more suggestive of an ongoing vasculitic process.

CONCLUSION

We described two cases of MPA with several unusual presenting characteristics. These patients both presented with acute respiratory failure secondary to DAH, both had isolated pulmonary involvement throughout their treatment course, and both patients were young adults at diagnosis. Consideration should be given to the diagnosis of MPA in a young patient presenting with acute respiratory failure secondary to DAH despite the atypical nature of their clinical presentations.

The opinions in this essay do not constitute endorsement by San Antonio Military Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, Department of Defense, or the U.S. Government of the information contained therein.

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REFERENCES

- Ntatsaki E, Watts R, Scott DGI. Epidemiology of ANCA-associated vasculitis. *Rheum Dis Clin North Am* 2010 Aug; 36(3): 447-61.
- Agard C, Mouthon L, Mahr A, Guillemin L. Microscopic polyangiitis and polyarteritis nodosa: how and when do they start? *Arthritis Rheum*. 2003 Oct 15; 49(5): 709-15.
- Gómez-Puerta J, Hernández-Rodríguez J, López-Soto A, Bosch X. Antineutrophil cytoplasmic antibody-associated vasculitides and respiratory disease. *Chest* 2009 Oct; 136(4): 1101-11.
- Gaffo A. Diagnostic approach to ANCA-associated vasculitides. *Rheum Dis Clin North Am* 2010 Aug; 36(3): 491-506.
- Chung S, Seo P. Microscopic polyangiitis. *Rheum Dis Clin North Am* 2010 Aug; 36(3): 545-58.
- Collins C, Quismorio F. Pulmonary involvement in microscopic polyangiitis. *Curr Opin Pulm Med* 2005 Sep; 11(5): 447-51.
- Homma S, Suzuki A, Sato K. Pulmonary involvement in ANCA-associated vasculitis from the view of the pulmonologist. *Clin Exp Nephrol* 2013 Oct; 17(5): 667-71 .
- Seo P, Stone J. The antineutrophil cytoplasmic antibody-associated vasculitides. *Am J Med* 2004 Jul 1; 117(1): 39-50.
- Kim J, Park J, Wang Y, Park H, Sung S, Kim D. Diffuse Alveolar Hemorrhage in a 39-year-old Woman: Unusual Initial Presentation of Microscopic Polyangiitis. *Korean J Thorac Cardiovasc Surg* 2011 Dec; 44(6): 448-51.
- Bosch X, Font J, Mirapeix E, Revert L, Ingelmo M, Urbano-Marquez A. Antimyeloperoxidase Autoantibody-associated Necrotizing Alveolar Capillaritis. *Am Rev Respir Dis* 1992 Nov; 146(5 Pt 1): 1326-9.
- Bosch X, Lopez-Soto A, Mirapeix E, Font J, Ingelmo M, Urbano-Marquez A. Antineutrophilic Cytoplasmic Autoantibody - Associated Alveolar Capillaritis in Patients Presenting with Pulmonary Hemorrhage. *Arch Pathol Lab Med* 1994 May; 118(5): 517-22.
- Shorr A, Scoville S, Cersovsky S, Shanks G, Ockenhouse C, Smoak B, et al. Acute eosinophilic pneumonia among US Military personnel deployed in or near Iraq. *JAMA* 2004 Dec 22; 292(24): 2997-3005.
- Laque D, Cadranel J, Lazor R, Pourrat J, Ronco P, Guillemin L, et al. Microscopic Polyangiitis with Alveolar Hemorrhage. A study of 29 cases and review of the literature. *Medicine (Baltimore)* 2000; 79(4): 222-33.
- Porres-Aguilar M, Figueroa-Casas J, Porres-Muñoz M, Elliott C. A 38-year-old pregnant woman with hemoptysis and acute renal failure. *Microscopic polyangiitis*. *Respiration* 2011 Jan; 82(1): 60-4.
- Milne K, Stanley K, Temple R, Barker T, Ross C. Microscopic polyangiitis: first report of a case with onset during pregnancy. *Nephrol Dial Transplant* 2004 Jan; 19(1): 234-7.
- Arulkumaran N, Jawad S, Smith S, Harper L, Brogan P, Pusey C, et al. Long-term outcome of paediatric patients with ANCA vasculitis. *Pediatr Rheumatol Online J* 2011 Jun 19; 9: 12.
- Yalcindag A, Sundel R. Vasculitis in childhood. *Curr Opin Rheumatol* 2001 Sep; 13(5): 422-7.
- Siomou E, Tramma D, Bowen C, Milford D. ANCA-associated glomerulonephritis/systemic vasculitis in childhood: clinical features-outcome. *Pediatr Nephrol* 2012 Oct; 27(10): 1911-20.
- Ellis E, Wood E, Berry P. Spectrum of disease associated with antineutrophil cytoplasmic autoantibodies in pediatric patients. *J Pediatr* 1995 Jan; 126(1): 40-3.
- Bosch X, Mirapeix E, Font J, Cervera R, Ingelmo M, Khamashta M, et al. Anti-myeloperoxidase autoantibodies in patients with necrotizing glomerular and alveolar capillaritis. *Am J Kidney Dis* 1992 Sep; 20(3): 231-9.
- Bosch X. Microscopic polyangiitis (microscopic polyarteritis) with late emergence of generalised Wegener's granulomatosis. *Ann Rheum Dis* 1999 Oct; 58(10): 644-7.
- Flores-Suárez L. Limited pulmonary MPA, a new MPA entity? A rheumatologist's perspective. *Clin Exp Nephrol* 2013 Oct; 17(5): 672-5.
- Mahr A, Moosig F, Neumann T, Szczeklik W, Taillé C, Vaglio A, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolutions in classification, etiopathogenesis, assessment and management. *Curr Opin Rheumatol* 2014 Jan; 26(1): 16-23.
- Sugino K, Kikuchi N, Muramatsu Y, Sano G, Kusano E, Isobe K, et al. Churg-Strauss Syndrome Presenting with Diffuse Alveolar Hemorrhage and Rapidly Progressive Glomerulonephritis. *Intern Med* 2009; 48(20): 1807-11.
- Lai R, Lin S, Lai N, Lee P. Churg-Strauss syndrome presenting with pulmonary capillaritis and diffuse alveolar hemorrhage. *Scand J Rheumatol* 1998 Jan; 27(3): 230-2.
- Sakamoto S, Kaburaki K, Gocho K, Ishida F, Sakaguchi S, Satoh K, et al. Azithromycin-induced diffuse alveolar hemorrhage. *J Japanese Respir Soc* 2009 Apr; 47(4): 337-41.