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Double edge sword

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAVs) are characterized blood vessel inflammation and necrosis which may lead to diffuse alveolar hemorrhage (DAH) resulting in life threatening respiratory failure. We present a case of microscopic polyangiitis presented in respiratory failure secondary to DAH that developed a rare treatment related complication. A 50 year old lady presented in respiratory failure with hemoptysis & falling hemoglobin. Chest X-ray showed bilateral inhomogeneous opacities and urine showed granular casts and red blood cells. Red colored bronchoalveolar lavage was obtained and serology came positive for pANCA. She was treated with corticosteroid and rituximab. The patient improved initially, but later developed rituximab induced late onset neutropenia. She unfortunately developed pulmonary mucormycosis and could not be revived. Thus, rituximab behaved as a "double edge sword", helping the patient initially but later making her susceptible for opportunistic infection.

Keywords: ANCA associated vasculitis (AAV); Diffuse alveolar hemorrhage (DAH); Microscopic polyangiitis (MPO); Rituximab; Neutropenia.

Introduction

Acute respiratory failure is one of the most serious emergencies that needs urgent and intense management. A wide range of diseases result in respiratory failure ranging from infections to systemic diseases. Diffuse alveolar hemorrhage (DAH) is one such entity that can result inlife threatening respiratory failure. DAH is considered as one of the most serious consequences of anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAVs), which are characterized by blood vessel inflammation and necrosis [1,2]. Diagnosing AAV itself is a challenging task, treatment regimens using immunosuppressants and corticosteroids further complicates the management. We present a case of microscopic polyangiitis (MPA) presented in respiratory failure secondary to DAH that developed a rare treatment related complication.

Case presentation

History

In pre-COVD era, a 50-year-old lady came with complaints of four days fever with dyspnea at rest, dry cough and streaky hemoptysis. She had hypertension and hypothyroidism. There was no significant medical/surgical illness in past. On physical examination, she had tachycardia (pulse – 140/min), tachypnea (respiratory rate – 40/minute) and SpO_2 of 80% on 6 liters O_2/minute. There were fine crepitations bilaterally on respiratory system examination. Other systems were within normal limits.

Investigations

She was taken to intensive care unit and started on non-invasive ventilation. At the time of admission, her chest X-ray

showed bilateral inhomogeneous opacity in midzone/ lower-zone (Figure 1a) and the blood investigation showed anemia & raised levels of urea/creatinine. The following day, her chest X-ray worsened (involved bilateral upper lobes) (Figure 1b), hemoglobin dropped, creatinine further increased and urine showed presence of albumin, granular casts and red blood cells (Table 1). Her microbiological work up for common infective pathogens (of sputum and blood) was negative (Table 2). The Procalcitonin and NT pro-BNP levels were normal. However, her perinuclear anti neutrophil cytoplasmic antibody (p-ANCA) came positive. Fiber optic bronchoscopy was performed and hemorrhagic bronchoalveolar lavage was obtained which confirmed diffuse DAH (Figure 2). Ultrasound guided kidney biopsy was attempted, but the patient developed hematoma. The histopathology report showed presence of few globally sclerosed glomeruli with intraglomerular fibrosis, periglomerular inflammation and bowman's capsule rupture.

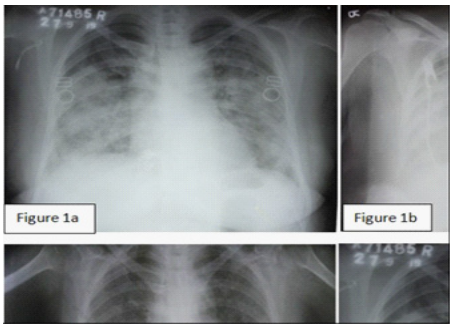

Figure 1: Chest X-ray of the patient depicting the clinical course. (1a) Bilateral inhomogeneous opacity at the time of admission. (1b): Increase in opacities with involvement of upper zones on next day. (1c) Resolution of opacities on starting treatment. (1d) Reappearance of bilateral inhomogeneous opacities at the time of R-LON.

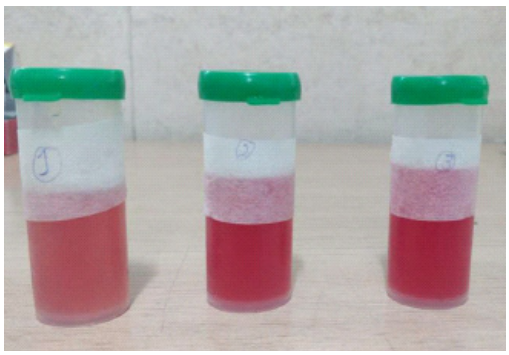

Figure 2: Red coloured bronchoalveolar lavage. The redness increasing with each aliquot.

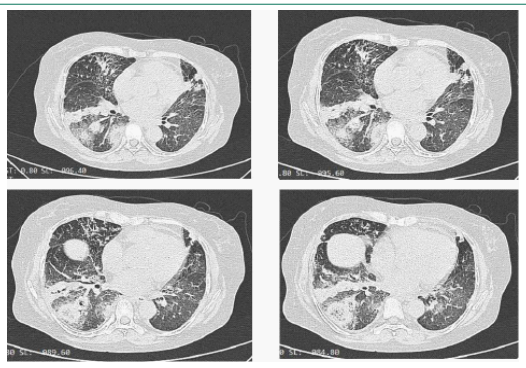

Figure 3: HRCT chest images showing reverse halo sign (Atoll sign).

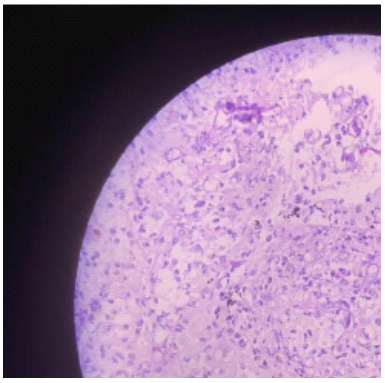

Figure 4: Photomicrograph of trans thoracic lung biopsy showing mucormycosis.

Table 1: Table showing routine blood investigations over initial 3 days.

	On Admission	Day 1	Day 2	Day 3
Hb	8.1gm/dl	7.2 gm/dl	7.0 gm/dl	7.2 gm/dl
TLC	7400/mm^3	5,300/mm^3	4,300/mm^3	7,200/mm^3
DLC		N96 M3 E1		
Platelet	2,09,000/ mm^3	2,69,000/ mm^3	2,34,000/ mm^3	2,71,000
RBS	107mg/dl	100mg/dl		
Urea	80 mg/dl	89 mg/dl	79mg/dl	68 mg/dl
Creatinine	1.5 mg/dl	1.6 mg/dl	1.4mg/dl	1.6 mg/dl
Na^+/K^+	138/4.2	134/4.3	136/3.5	135/4.5
T. Billi	0.7	0.8 mg/dl	1.1 mg/dl	1.2 mg/dl
AST/ALT		41/23 IU/L		44/53 IU/L
Urine R/M		Albumin +, RBC +, Granular casts +		Alb – 2+, RBC +, Granular casts +

Table 2: Table showing microbiological work up and serology.

Sputum for gram stain	Negative
Sputum for bacterial culture	Negative
Sputum for CBNAAT	Negative
Blood cultures	Negative
HIV 1& 2	Negative
H1N1 RT-PCR	Negative
Serology for malaria, dengue & leptospira	Negative
ANA	Negative
pANCA	**Positive**

Diagnosis

The patient was diagnosed Microscopic Polyangiitis in view of: 1) Presence of ANCA associated small vessel vasculitis. 2) MPO-ANCA (p-ANCA) – positive. 3) Primary involvement of

lungs and kidney. 4) Absence of characteristic features of granulomatosis with polyangiitis (GPA) (like upper airway involvement, c-ANCA etc). Final diagnosis made was "acute respiratory failure secondary to diffuse alveolar hemorrhage in a case of generalized microscopic polyangiitis (AAV) with a BVAS score of 5".

The patient was initially stabilized with non-invasive ventilation (NIV) with high FiO_2. She was given broad spectrum intravenous antibiotics and blood transfusions. Treatment of AAV was as per European League Against Rheumatism (EULAR) guidelines [3]. As the patient had life threatening end organ damage in form of diffuse alveolar hemorrhage, induction of remission was done with steroid (methylprednisolone 1 gm intravenous for 5 days followed by 60 mg once daily (oral) x 1 month) and intravenous rituximab (RTX) (500 mg once a week x 1 month). Patient responded to initial treatment.

Outcome & complications

The patient improved after 1 week and respiratory failure resolved (Figure 1c). She was continued on weekly dose of RTX (375 mg/m^2 per week for 4 weeks) and was being regularly montored. After 2 weeks of her 4th dose of RTX she was found to have neutropenia (absolute neutrophil count of 1,100/mm^3). This rituximab induced late onset neutropenia (R-LON) was managed with granulocyte monocyte – colony stimulating factor (GM-CSF). The patient got readmitted because of fever, dyspnea and low oxygen saturation. There were bilateral inhomogeneous opacities on X-ray chest (Figure 1d). High resolution computed tomography (HRCT) showed bilateral consolidation and presence of reverse halo sign (Atoll sign) (Figure 3). Her transthoracic lung biopsy showed mucormycosis (Figure 4). However, patient developed multiorgan dysfunction and could not be revived.

Discussion

ANCA associated vasculitides are characterized by typical pathological lesions in vessels produced by ANCAs. As per the 2012 Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC 2012), AAVs have necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles and smallarteries) [4]. Lungs get frequently involved in AAVs and commonly lead to DAH [2]. Pathologically, DAH is defined by the presence of cellular inflammation, tissue necrosis, vessel destruction leading to organ dysfunction. Kidneys also get invariably involved in AAVs in form of pauci-immune necrotizing and crescentic glomerulonephritis. Our patient presented in respiratory failure and it was important to find out the underlying cause. Her work up for the common causes of respiratory failure came negative which puzzled us initially, however the serially dropping haemoglobin and presence of albumin & granular casts in urine pointed towards vasculitis. The bronchoalveolar lavage in our patientwas red coloured and the redness increased with each aliquot. This is considered as diagnostic of DAH [5,6]. Early bronchoscopy to demonstrate alveolar haemorrhage and rule out infection is advised in patients of DAH. The characteristic feature of AAV is the presence of antineutrophil cytoplasmic autoantibodies (ANCA). Based on the indirect immunofluorescence pattern, they are divided into two types – i) perinuclear (p-ANCA) and ii) cytoplasmic (c-ANCA) patterns [7,8]. The autoantigen for p-ANCA is myeloperoxidase (MPO) and for c-ANCA it is proteinase 3 (PR3). 95% of new onset granulomatosis with polyangiitis (GPA) have c-ANCA. 80% ofnew onset microscopic polyangiitis (MPA) and only 40% of eosinophilic granulomatosis with polyangiitis (EGPA) have p-ANCA [8-10]. In most cases a confident diagnosis may be made without tissue biopsy [7,8]. Easily accessible sites such as the skin or upper airway lesions are targeted for diagnostic biopsy. Our patient had DAH and kidney involvement but there were no skin or upper airway lesions. Small specimen size and architectural disruption, makes the utility of transbronchial biopsy controversial [2,11]. Hence, kidney biopsy was attempted under ultrasound guidance, but the patient developed hematoma and the small tissue pieces obtained were not diagnostic. The patient was diagnosed microscopic polyangiitis as she had positive (p-ANCA) with primary involvement of lungs and kidney and absence of characteristic features of GPA like the upper airway involvement, c-ANCA etc [10,12,13]. The treatment for AAV is complex and involves close monitoring. As per the European Vasculitis Study Group (EUVAS)[14] criteria our patient had "generalized" disease with Birmingham vasculitis assessment score (BVAS) [15] of "5". EULAR recommendations were followed for the management [3]. She had life threatening end organ failure in form of DAH, so the remission of induction was started with combination of glucocorticoids and rituximab. Corticosteroids with immunosuppressants are needed for induction of remission. In severe disease pulse steroid therapy (intravenous methylprednisolone 500-1000 mg/day) for 3 days followed by prednisone 1 mg/kg/day (max 80 mg/day)) may be considered [16]. Two alternatives of immunosuppressants are considered for induction of remission – cyclophosphamide (CYC) & rituximab (RTX). RTX is a chimeric monoclonal antibody directed against the CD20+B-cell antigen and offers a more specific and targeted approach to B-cell driven disorders. The RAVE and the RITUXIVAS trials compared CYC & RTX for induction of remission in AAV and it was concluded that RTX was not inferior to CYC for the induction of remission in severe AAV and had a better side effect profile [17,18]. Based on this remission induction in our patient was done with RTX in a dose of 375mg/m^2 once a week for 4 weeks along with corticosteroids.

The patient initially improved and was being closely montitored. She was found to have neutropenia (absolute neutrophil count (ANC) -1,100/mm^3) at 6 weeks i.e., 2 weeks after receiving 4th dose of RTX (once a week). RTX has been reported to cause neutropenia with a delayed and often unpredictable onset. Rituximab associated late-onset neutropenia (R-LON) has been defined as neutropenia developing at least three to four weeks following rituximab administration [19]. This may occur in 8% to 27% of patients treated with RTX. The exact mechanism has yet to be fully elucidated; however, a variety of theories exist. After RTX administration, antibodies against neutrophils may be produced, resulting in neutropenia [21]. It may also develop due to aberrant B-cell reconstitution after RTX administration [21]. Mostcases of R-LON are self-limiting and resolve without any complications. The incidence, magnitude, and duration of neutropenia is shown to be reduced by granulocyte-colony stimulating factors (G-CSFs). Without the utilization of G-CSFs, R-LON may last a median of 6 to 77 days [22-25]. The patient got readmitted in respiratory failure and was found to have pulmonary mucormycosis on lung biopsy. This was an opportunistic infection contracted because of neutropenia which was in turn caused by rituximab. Thus, rituximab acted as a "double edge sword", initially helping in treating AAV but later causing neutropenia. To the best of ourknowledge this is the first case reported from India where rituximab caused neutropenia in AAV and made the patient susceptible to pulmonary mucormycosis.

Conclusion

Acute respiratory failure secondary to systemic diseases like AAVs have life threatening DAH and needs urgent attention. Immunosuppressants have their own risks and benefits; and may act like a "double edge sword". Thus, it is important to diagnose the exact cause of respiratory failure, start appropriate treatment and closely monitor the patient for the entire treatment duration.

References

1. Lapraik C, Watts R, Bacon P, Carruthers D, Chakravarty K, D'Cruz D et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology (Oxford) 2007; 46: 1615-6.
2. Park MS. Diffuse Alveolar Hemorrhage. Tuberc Respir Dis. 2013; 74: 151-62.
3. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T et al. EULAR/ERAEDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016; 75: 1583-94.
4. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013; 65: 1-11.
5. Jennette JC, Patrick H, Nachman PH. ANCA Glomerulonephritis and Vasculitis. Clin J Am Soc Nephrol. 2017; 12: 1680-91,
6. Colby TV, Fukuoka J, Ewaskow SP, Helmers R, Leslie KO. Pathologic approach to] pulmonary hemorrhage.Ann Diagn Pathol. 2001; 5: 309-19.
7. Fijołek J & Wiatr E. Antineutrophil cytoplasmic antibodies (ANCA) – their role in pathogenesis, diagnosis, and treatment monitoring of ANCA-associated vasculitis.Cent Eur J Immunol. 2019; 45: 218-27.
8. Falk RJ & Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing andcrescentic glomerulonephritis. N Engl J Med. 1988; 318: 1651-7.
9. Niles JL, McCluskey RT, Ahmad MF & Arnaout MA. Wegener's granulomatosis autoantigen is a novel neutrophilserine proteinase. Blood. 1989; 74: 1888-93.
10. Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum. 2005; 52: 2926-35.
11. Schnabel A, Holl-Ulrich K, Dalhoff K, Reuter M, Gross WL. Efficacy of transbronchial biopsy in pulmonary vaculitides. Eur Respir J. 1997; 10: 2738-43.
12. Chung SA & Seo P. Microscopic Polyangiitis. Rheum Dis Clin North Am. 2010; 36: 545-58.
13. Radice A & Sinico RA. Antineutrophil cytoplasmic antibodies (ANCA). Autoimmunity. 2005; 38: 93-103.
14. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009; 68: 310-317.
15. Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum. 2001; 44: 912-920.
16. McGeoch L, Twilt M, Famorca L, Bakowsky V, Barra L, Benseler SM et al. CanVasc Recommendations for the Management of Antineutrophil Cytoplasm Antibodyassociated] Vasculitides. The Journal of Rheumatology. 2016; 43: 97-120
17. Stone JH, Merke PA, Spiera R, Seo P, Langford CA, Hoffman GS et al. Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis. N Engl J Med. 2010; 363: 221-32.
18. Jones RB, Tervaert JWC, Hauser T, Luqmani R, Morgan MD, Peh CA et al. Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. N Engl J Med. 2010; 363: 211-20.
19. Moore DC. Drug-Induced Neutropenia. A Focus on Rituximab-Induced Late-Onset Neutropenia. Pharmacovigilance forum. 2016; 40: 765-8.
20. Yamazaki M, Sugiura H, Iwatani Y, Nokiba H, Amemiya N, Nitta K et al. Late-Onset Neutropenia after Rituximab Treatment for Adult-Onset Nephrotic Syndrome. Case Reports in Nephrology. 2019; 2019: 1-4.
21. Chaiwatanatorn K, Lee N, Grigg A, Filshie R and Firkin F. Delayed-onset neutropenia associated with rituximab therapy. British Journal of Haematology. 2003; 121: 913-8.
22. Salmon JH, Cacoub P, Combe B, Sibilia J, Pallot-Prades B, Fain O et al. Late-onset neutropenia after treatment with rituximab for rheumatoid arthritis and other autoimmune diseases: data from the autoimmunity andrituximab registry. RMD Open. 2015; 1: e000034.
23. Reitblat O, Wechsler A, and Reitvlat O. Rituximab-related late-onset neutropenia in patients with rheumatic diseases: successful re-challenge of the treatment. American Journal of Case Reports. 2015; 16: 211-4.
24. Wolach O, Bairey O and Lahav M. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. Medicine 2010; 89: 308-18.