Review Article

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Diffuse alveolar hemorrhage and intravascular hemolysis due to acute mitral valve regurgitation

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Abstract

Diffuse alveolar hemorrhage (DAH) is a life-threatening condition that complicates various clinical entities. While mitral stenosis is a well-known cardiovascular cause, acute mitral regurgitation (MR) related DAH is rarely reported. We report a patient with a stormy course of acute MR induced DAH with concomitant Coomb's negative intravascular hemolysis, which resolved completely after mitral valve surgical repair.

Key words: Acute mitral regurgitation, diffuse alveolar hemorrhage, intravascular hemolysis.

Case

A 50-year-old man with history of hypertension, chronic mild renal impairment was admitted with fever, hemoptysis, shortness of breath and left side chest pain for 2 days. Physical examination on admission was unremarkable except mild basal crepitations on auscultation. Chest radiograph showed bilateral alveolar infiltrates (**Figure 1**). Electrocardiogram showed a sinus rhythm with right bundle branch block. The initial impression was community-acquired pneumonia and he was prescribed amoxicillin/clavulanate. His conditions deteriorated and he subsequently required mechanical ventilation and veno-venous extracorporeal membrane oxygenation (ECMO) because of refractory hypoxemic respiratory failure. Urgent thoracic computed tomography showed diffuse patchy peribronchovascular and centrilobular ground glass opacities and consolidations in all lobes of lungs, which were non-specific (**Figure 2**). Bedside transthoracic echocardiogram revealed mild mitral regurgitation with normal systolic function and no regional wall motion abnormality. He was further complicated by acute on chronic renal failure necessitating continuous renal replacement therapy.

Antibiotics were upgraded empirically to piperacillin/tazobactam, doxycycline and oseltamivir. Microbiological workups including nasopharyngeal aspirate immunofluorescence for common respiratory viruses, viral culture, sputum culture, sputum acid-fast stain, antibodies to rickettsia, hantavirus, leptospira were all negative. Serological studies included rheumatoid factor, antinuclear antibody, antineutrophilic cytoplasmic antibody (ANCA), antiglomercular basement membrane antibody (anti-GBMA) revealed negative. Bronchoscopy confirmed progressively hemorrhagic lavage return and abundant hemosiderin laden macrophages. Bronchial aspirate culture was negative.

The patient improved with supportive management with no more hemoptysis and was able to wean off veno-venous ECMO and ventilatory support subsequently. However, he deteriorated again two days after extubation with recurrent

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hemoptysis and worsening bilateral pulmonary infiltrates on chest radiographs. Pulmonary renal syndrome was suspected and he was prescribed pulse methylprednisolone. Subsequent open lung biopsy showed focal intra-alveolar hemorrhage with no evidence of vasculitis, granuloma or hyaline membrane formation. Stainings for microorganisms were negative. The lung biopsy specimen was put into formalin and further immunological staining was not possible to rule out Goodpasture syndrome. Despite the steroid therapy, the patient developed recurrent episodes of life-threatening pulmonary hemorrhage. Eight sessions of plasmapheresis were subsequently given. Hematological studies one month post admission also revealed a concomitant Coomb's-negative intravascular hemolytic anemia. Screening for paroxysmal nocturnal hemoglobinuria, cold agglutinins, cryoglobulin were all negative. Repeated blood transfusions were needed. Reassessment transthoracic echocardiogram on day 28 revealed normal left ventricular systolic function with moderate eccentric mitral regurgitation. After initiation of metoprolol for heart rate control, the rate of hemolysis improved (**Figure 3**).

Subsequent renal biopsy only showed features of hypertensive glomerulosclerosis, which ruled out Goodpasture syndrome. Steroid therapy was gradually tapered off. Repeated transthoracic echocardiogram revealed flail posterior mitral valve leaflet and severe MR with an anterior directing jet. Chambers sizes were within normal range. There was no significant left ventricular outflow tract gradient. Transesophageal echocardiogram showed flail mitral valve (P3 scallop) due to ruptured chordae with severe MR. There was no evidence of infective endocarditis. Open heart valvulopasty of mitral valve was subsequently performed. After the operation, the patient completely recovered from recurrent pulmonary hemorrhage and hemolysis and his renal function returned back to baseline and he was able to wean off oxygen supplement and dialysis support.

Discussion

DAH is characterized by dyspnea and bilateral diffuse alveolar infiltrates on chest X-ray. Hemoptysis is usually but not always present. Anemia and the return of hemorrhagic lavage during bronchoscopy support the diagnosis. The causes of DAH can be classified into vasculitis related, "bland" pulmonary hemorrhage and alveolar hemorrhage related to other conditions like diffuse alveolar damage. The presence of acute renal failure may point to pulmonary-renal syndrome resulting from vasculitis like Wegener's granulomatosis, microscopic polyangiitis or Goodpasture syndrome. Exposure to drugs like propylthiouracil, penicillamine can also offer diagnostic clues. Cardiac causes of DAH are proposed to be due to mechanical pressure intolerance of pulmonary microcirculation. (1) While mitral stenosis is widely known for causing DAH, acute MR is rarely reported.

Unlike chronic MR, which is usually asymptomatic until development of left ventricular failure, acute MR has a devastating presentation of cardiogenic shock. The abrupt increase in left atrial pressure also leads to pulmonary edema and possibly, disruption of alveolar capillary membrane or rupture of submucosal bronchial varices. The DAH in acute MR like this case was very rare and only 3 case reports were published so far. (1-3)

Transthoracic echocardiography is indispensible to assess MR severity. However, the quality is often limited by poor echogenicity or when dealing with heavily calcified or mechanical valves. This is especially true in critically ill, mechanically ventilated patients. Semiquantitative assessment based on Doppler color flow mapping often underestimates MR severity because of eccentric jet or aliasing artifact. (4) Moreover, in acute MR, the tachycardia, the systemic hypotension, the poorly compliant left atrium and the resultant rapid augmentation of left atrial pressure all lead to smaller regurgitant jet area during echocardiography, like in this case. Quantitative measures of regurgitant severity like effective regurgitant orifice area and regurgitant volume that are useful in chronic regurgitation can be inaccurate in acute regurgitation. (4) Serial reassessments are necessary. Due to the close proximity between the ultrasound transducer and mitral valve apparatus, transesophageal echocardiography should be considered if there is clinical suspicion. It provides much better imaging quality and gives incremental information like the cause and mechanism of acute MR and the reparability.

Mechanical intravascular hemolysis had been well documented after mechanical prostheses replacement and mitral valve repair. (5-7) It is attributed to shearing stress on the erythrocytes in turbulent flow. (6,8). Suggested

mechanisms include collision and the rapid deceleration of the regurgitant jet into the prosthetic or annuloplasty ring, fragmentation of the regurgitant jet by a dehisced annuloplasty ring or rupture chord, and rapid acceleration of a jet through a small orifice like a small para-ring channel. (9) Our case is probably the first reported case of mechanical intravascular hemolysis secondary to severe MR in a native heart valve. By reducing heart rate and left ventricular contractile force using beta-blocker, shearing stress was lowered and the rate of hemolysis improved. Similar clinical benefit of beta-blocker had been reported by Aoyagi in a patient with hemolysis due to paraprosthetic leakage and by Kubo in a patient suffering from hypertrophic obstructive cardiomyopathy with hemolylsis due to sky-high left ventricular outflow tract gradient. (8,10)

Our case illustrated that acute MR can be a rare cause of diffuse alveolar hemorrhage and intravascular hemolysis. This should be considered when usual diagnostic studies fail to uncover a specific cause. Early transesophageal echocardiography should be considered when conventional transthoracic study is inconclusive.

Figure 1. Chest radiography on admission showed bilateral alveolar infiltrates

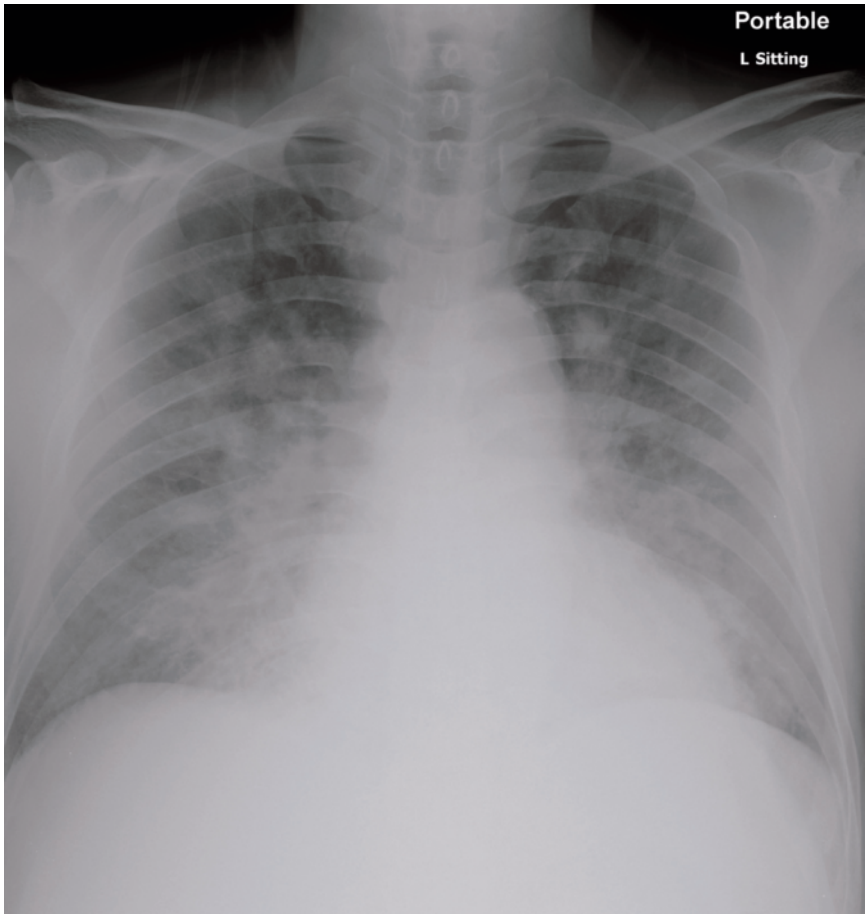


Figure 2. Thoracic CT showed bilateral patchy peribronchovascular and centrilobular ground glass opacities and consolidations in all lobes of the lungs, which were non-specific and may represent infection, inflammation or hemorrhage

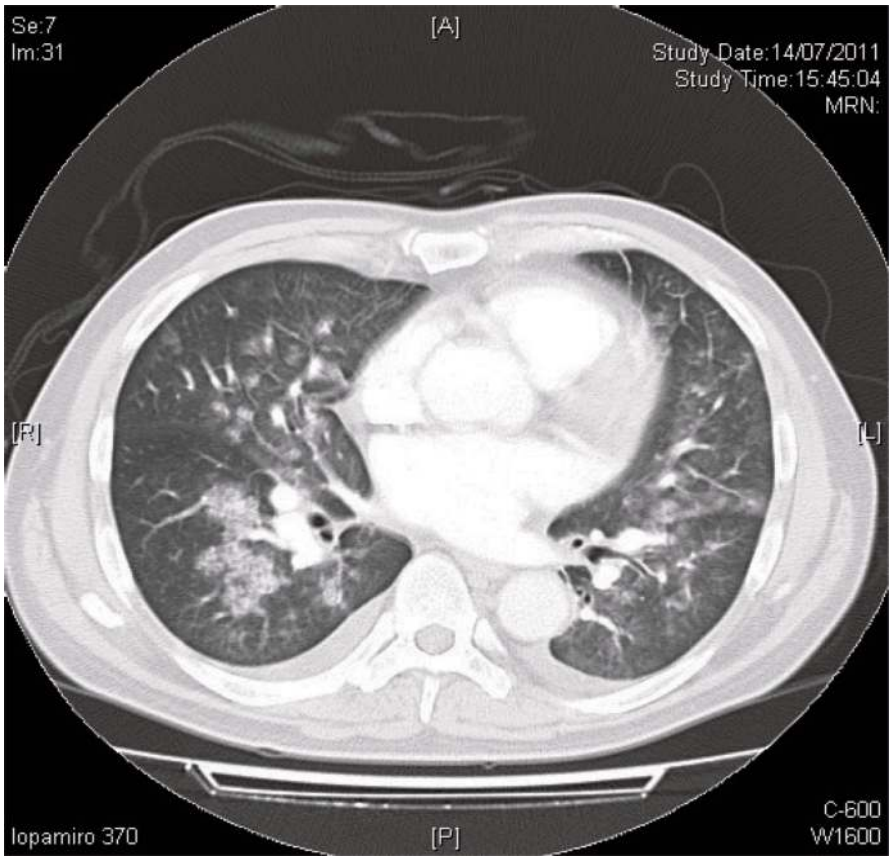
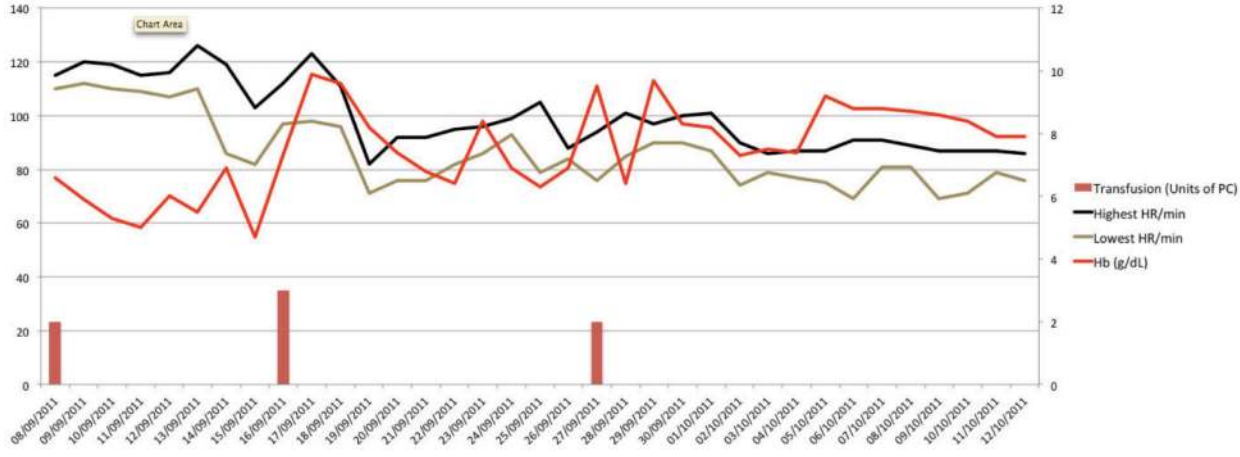


Figure 3. Hemoglobin drops were noted after days of tachycardia and it remained relatively static after full metoprolol blockage since 4/10/2011



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