Hyepereosiniphilic syndrome and COVID-19 pandemic: 2 case reports

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Case Report

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Abstract

Background

Nearly half of the patients with hypereosinophilic syndrome (HES) have cardiovascular involvement, a major cause of mortality. COVID-19 infection can lead to cardiac involvement, negatively impacting the clinical course and prognosis. We reported two cases of HES with cardiac involvement resulting in valve replacement, which were complicated by COVID-19.

Case presentation:

Our first case was a 27-year-old woman admitted due to dyspnea and signs of heart failure. An echocardiogram revealed severe mitral stenosis and mitral regurgitation. Corticosteroid therapy resulted in the improvement of her symptoms. However, she deteriorated during her hospital course following a positive COVID-19 test. A repeated echocardiogram showed right ventricular failure with severe mitral regurgitation and torrential tricuspid regurgitation. Therefore, she underwent mitral and tricuspid valve replacement. Our second case was a 43-year-old man with HES resulted in severe tricuspid stenosis. Corticosteroid treatment improved tricuspid stenosis, but he underwent valve replacement due to severe valvular regurgitation. He was admitted following tricuspid prosthetic valve thrombosis. Initial workups revealed lung involvement in favor of COVID-19 infection, and his PCR test was positive.

Conclusion

COVID-19 pandemic can change the clinical course of HES. It may result in a heart failure exacerbation due to myocardial injury and an increased risk of thrombosis in prosthetic valves or native vessels due to hypercoagulability.

Background

Hypereosinophilic syndrome (HES) is defined as a high peripheral eosinophil count (> 1.5×10^9/L) along with evidence of eosinophil-related organ damage (1). The etiology can be neoplastic (primary), reactive to diseases like parasitic infection or lymphoma (secondary), and, more commonly, idiopathic (1). Cardiac involvement, known as "Loeffler's Endocarditis," can occur as a consequence and consists of three different phases: acute necrotic asymptomatic phase, thrombotic phase with possible embolic events, and fibrotic phase with restrictive cardiomyopathy and symptoms of heart failure (1, 2). Nearly half of the patients have cardiovascular involvement, a major cause of mortality in HES (3).

Over the past two years, millions have been affected by coronavirus disease 2019 (COVID-19). Although upper respiratory tract symptoms are the most common manifestations, myocardial injury can occur in many patients, ranging from myocarditis to acute heart failure and cardiogenic shock (4). Cardiac involvement has a negative impact on the clinical course and prognosis of COVID-19, especially in patients with pre-existing heart disease. COVID-19 also results in exacerbation of the compensated pre-existing cardiac diseases or increasing the complications (4). Herein, we describe two patients with HES complicated by COVID-19 and discuss the coagulation status and treatment strategies in such patients.

Case Presentation

Case 1

A 27 years old woman was admitted to our hospital for dyspnea at rest and fatigue. Her Symptoms gradually increased during the few weeks before admission. She also had nausea resulting in poor appetite and palpitation. In her past medical history, a history of controlled asthma with inhaled corticosteroid was present for ten years. Her habitual history was unremarkable. In physical examination, blood pressure was 100/60 mmHg, heart rate was 103 beats per minute, respiratory rate was 30 per minute, oral temperature was 36.7 C, and oxygen saturation was 96% in room air. Jugular venous pressure (JVP) was elevated, and a systolic murmur was heard in the lower left sternal border and cardiac apex. Breath sounds were reduced in the basal parts of the lungs. Bilateral lower limb pitting edema was detected in both legs.

In the initial lab data, complete blood count (CBC) with differential was as follows: hemoglobin (Hb) level was 12.7 g/dl, platelet count was 109000×10^9/L, and white blood cell (WBC) count was 13500×10^9/L mm3 with the Neutrophils and lymphocytes percentages equal to 49% and 12%, respectively. The eosinophil count was significantly high (4185×10^9/L, 31% of WBCs). Chest X-ray showed bilateral pleural effusion. Pleural fluid analysis showed a protein level of 1200 mg/dl, lactate dehydrogenase (LDH) level of 297 U/L, and albumin level of 800 mg/dl. Simultaneous blood sampling showed a serum LDH level of 558 U/L, serum total protein level of 6.4 g/dl, and serum albumin level of 3.6 g/dl. The results were in favor of a transudate effusion. Spirometry was performed based on the history of asthma, which showed a forced expiratory volume (FEV1) of 37%, forced vital capacity of 39%, and FEV1 to FVC ratio of 92%. The pattern was in favor of mixed obstructive and restrictive airway disease.

Cardiac auscultation findings and the presence of a transudate pleural effusion highlighted a cardiac etiology for her complaints. Echocardiography was performed in the next step, which showed a left ventricular ejection fraction (LVEF) of 55%. There was a significantly increased thickness in the ventricular side of mitral valve leaflets that was extended to the basal part of the ventricular endocardium, resulting in mass formation. The maximum diameter was about 20mm (Fig. 1). Severe functional mitral stenosis (MS) with a mean gradient of 16 mmHg and severe mitral regurgitation (MR) were detected. Slight obliteration of RV apex was evident with sparing of LV apex. Tricuspid valve leaflets were thickened and mal-coapted with severe tricuspid regurgitation (TR)

and no tricuspid stenosis. Inferior vena cava (IVC) was dilated with reduced respiratory collapse. Systolic pulmonary arterial pressure (PAP) was 43 mmHg. HES was considered the patient`s diagnosis regarding high eosinophil count and echocardiographic findings.

Extensive diagnostic workups were performed to elucidate the etiology of high eosinophil count, including peripheral blood smear (PBS) preparation and additional blood tests. PBS was unremarkable except for an elevated eosinophil count. Vitamin B12 level was 510 pg/mL (200–835 pg/mL). Other lab data were as follows: Creatinine level was 1.1 mg/dl, Aspartate aminotransferase (AST) level was 17 U/L, and alanine aminotransferase level was 25 U/L, Anti-nuclear antibody (ANA) level was 0.2 (< 1.0), C-anti neutrophilic cytoplasmic antibody (ANCA) level was 0.6 U/mL (< 18), P-ANCA level was 0.5 U/mL (< 18), and interferon-gamma release assay (IGRA) for tuberculosis was negative. Urine analysis was normal. Abdominal sonography showed normal liver and spleen size and echogenicity with mild to moderate ascites. Stool examination showed no parasite ova or larva. In bone marrow aspiration and biopsy, no evidence of malignancy or primary myeloproliferative disorder was detected. Evaluation for genetic translocation of BCR/ABL and ETV6-PDGFRB were also negative. The results were in favor of idiopathic HES. Results of the cardiac biomarkers were as follow: N terminal pro B type natriuretic peptide (NT-pro BNP) level was 46 pg/ml, and high sensitive troponin I (hs-CTnI) level was 0.015 mcg/L (< 0.12).

Corticosteroid therapy and intravenous heparin was initiated, and there was a relative improvement in symptoms after one week. WBC count and eosinophil percentage were decreased to 8000×10^9/L and 0.3%, respectively. However, clinical deterioration occurred during the hospital course and after initial improvement. The oxygen saturation was reduced to 80%. Chest CT scan showed ground glass opacification in favor of COVID-19. Nasopharyngeal swab polymerase chain reaction (PCR) was positive for SARS-COV-2. Erythrocyte sedimentation rate (ESR) was increased to 63 mm/h, and the D-dimer level was 830 mcg/L. Supportive medical therapy was initiated and continued for a week. However, systolic blood pressure was decreased to 80 mmHg with evidence of end-organ hypoperfusion that mandated administration of an intravenous inotropic agent (norepinephrine). Repeated bedside echocardiography showed significant right ventricular (RV) dysfunction with torrential TR and severe MR. As severe MR and torrential TR both played key roles in the clinical picture of the biventricular failure, the patient underwent cardiac surgery with bioprosthesis tricuspid and mitral valve replacement. After the surgery, she had an uneventful course of hospital stay and was discharged home after one week.

Case 2

A 43 years old man was admitted to our hospital in 2014 due to severe dyspnea and cough initiated one week before admission. Symptoms were exertional with New York Heart Association (NYHA) class III. The patient had been treated for asthma and chronic sinusitis for more than a decade. There was no history of fever or other constitutional symptoms. In physical examination, ascites and bilateral peripheral pitting edema were detected. Paracentesis showed high serum ascites albumin gradient (SAAG). WBC count was 22000×109/L, with a high eosinophil count (11000×109/L). Echocardiography showed an LVEF of 40%, prominent obliteration of RV apex and to a lesser degree LV apex, severe thickening of tricuspid valves with extension to the RV free wall resulting in severe tricuspid stenosis (TS) with a mean gradient of about 7 mmHg, and mild to moderate TR (Fig. 2, Videos S1-S3). Extensive thickening of pulmonary leaflets was also evident with no pulmonary hypertension. The IVC was plethoric.

Diagnosis of HES was made, and secondary causes of eosinophilia, including parasitic infections, myeloproliferative disorders, and rheumatologic diseases, were ruled out. Results of BCR/ABL translocation and ETV6-PDGFRB were negative. Corticosteroid therapy was initiated, resulting in eosinophil count decline and improvement in symptoms. Two months later, the follow-up echocardiogram revealed a severe TR with no evidence of TS (Fig. 2C), and the patient underwent tricuspid valve replacement with a mechanical bileaflet prosthesis. The decision to the placement of a mechanical valve was based on the patient's preference and despite the higher probability of valve thrombosis due to his underlying disease. He had been on warfarin 5 mg daily since then, and the international normalization ratio (INR) was in the therapeutic range (mean INR ~ 3). He had two episodes of mechanical valve thrombosis with minimal symptoms in the following 6 years that were detected in the routine follow-up echocardiograms and were treated with intravenous thrombolysis (both of the episodes occurred in the course of bridge therapy for non-cardiac surgery and a dental procedure).

In September 2020, the patient was admitted with severe dyspnea and peripheral edema. On physical examination, blood pressure was 110/80 mmHg, heart rate was 92 bpm, respiratory rate was 30/min, and the oral temperature was 37.8 C. Jugular venous pressure was elevated. Prosthetic valve sound was not heard clearly, and scattered crackles were heard during lung auscultation. Other examination findings were unremarkable. In the lab data, WBC count was 11830×109/L, Hb level was 13.7 g/dl, and platelet count was 185000×109/L. The eosinophil count was high (23%). Echocardiography showed an LVEF of 40%, fixed tricuspid prosthesis leaflets, and a significant RV dysfunction. Fluoroscopy was performed, which confirmed the fixation of both tricuspid prosthesis leaflets (Video S4-S5). The INR was 1.84 (the previous documented INR one month before admission was 3, and the patient did not change his warfarin dose, start a new medication, or change his diet since then). Cardiac biomarkers were as follows: NT-pro BNP was 3832 pg/mL, and hs-CTnI was 0.096 mcg/L. Other lab data were as follows: creatinine level was 1.4 mg/d, ANA was 0.2, C- ANCA was 0.9 U/mL, P-ANCA was 12.5 U/mL, and sputum smear was negative for tuberculosis. Abdominal sonography showed normal liver and spleen size and echogenicity.

There was a high suspicion of pulmonary embolism from tricuspid valve thrombosis as the etiology of the patient

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s normal oxygen saturation and stable hemodynamics. The eosinophil count declined, and the patient underwent an elective redo tricuspid valve surgery after his PCR test became negative. The post-operation course was uncomplicated, and the patient was discharged one week after surgery.

Discussion

Heart failure symptoms can be the cardiac manifestation of HES (5), and dyspnea can be seen in more than half of the patients (5). The symptoms can be due to fibrosis replacement resulting in the development of restrictive cardiomyopathy (1). Valvular involvement is another etiology, as in our first patient. Atrioventricular valves are more commonly involved. Entrapment of subvalvular apparatus by thrombosis or fibrosis leads to restriction of valve motion and,

consequently, valvular regurgitation (2, 5). Valvular stenosis can also occur as a result of the extension of thrombosis into the atrioventricular valve orifice (2), although the prevalence is much less than valvular regurgitation (5). Our second patient was initially presented with tricuspid stenosis, which is a rare valvular involvement in HES.

Choosing a treatment strategy for HES depends on the underlying etiology. This necessitates a full diagnostic workup before initiating any treatments. Diagnostic workups include CBC with differential, stool exam for helminthic infection, serum B12 level (increased in myeloid etiology), flow cytometry, PBS, translocations like BCR/ABL and JAK2, and PDGFR mutations (6, 7). Specific considerations are needed based on the test results. Patients with PDGFR mutations respond well to imatinib (7, 8), and initiation of corticosteroid in a patient with Strongyloides can result in a disseminated helminth infection (3, 6). If no specific underlying condition is found in the diagnostic tests, as in our patients, a corticosteroid is the first line treatment of idiopathic HES (3, 8). Corticosteroids can result in the reduction of eosinophil counts and the prevention of further organ damage (6). Our patients had a good initial response to corticosteroid therapy, and their eosinophil counts had declined. Corticosteroids were especially effective in our second patient. During his first admission, the drug resulted in regression of the TS, which was a unique response not reported before. The valvular structures were damaged, and the patient eventually needed surgery due to the remaining TR, but the surgery was an elective one after the resolution of symptoms and reduction of the eosinophil count. The drug was also safe and effective in the last admission with concomitant COVID-19, resulting in a stable clinical course and improvement. In our first patient, however, the valvular regurgitations led to hemodynamic compromise following initial improvement. This compromise was possibly due to COVID-19 infection resulting in further structural damages by intensifying myocardial inflammation.

There are reports about regression of mitral regurgitation following corticosteroid therapy in HES (9). As was mentioned above, our second patient had a regression of tricuspid stenosis following medical therapy, which has not been reported previously. Therefore, it seems rational to consider a trial of medical therapy including corticosteroids in HES patients with severe valvular involvement (including valvular stenosis) and stable hemodynamics before referring them for surgery. However, surgical correction should be considered in the case of severe valvular involvement with significant hemodynamic decompensation despite initial medical treatment.

The American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the management of valvular heart disease indicates that in patients < 50 years old who require aortic valve replacement or < 65 years old who require mitral valve replacement, a mechanical valve is preferred over bioprosthesis if there is no contraindication for anticoagulant therapy (10). However, in patients with HES, prosthetic valve selection is not this simple. High eosinophil count and tissue damage in HES can result in a hypercoagulability state (3), which can increase the risk of thrombosis in mechanical valves. It is recommended to use bioprosthetic valves in patients with HES who require valve replacement despite the higher probability of valve degeneration and the need for future redo surgeries (1, 5). It is also recommended to start warfarin with a therapeutic INR range after bioprosthesis implantation to reduce the risk of prosthetic valve thrombosis further. Our first patient accepted to have bioprosthetic mitral and tricuspid valves, but our second patient didn`t accept the risk of redo surgery and had a mechanical tricuspid valve. He had three episodes of prosthetic valve thrombosis after the surgery, which shows the risk is real.

High eosinophil count can increase the expression of tissue factor (released from eosinophil granules) and a decrease in thrombomodulin (by proteins secreted from their granules) (5, 7). The result can be the activation of the coagulation cascade and hypercoagulability state (3). The tissue factor has a major role because it can activate factor VII and increase the fibrinogen level (5). However, despite the hypercoagulability state, there is no specific guideline on initiating prophylactic or therapeutic anticoagulation in HES (11). There are case reports of portal venous thrombosis (11), deep venous thrombosis, and pulmonary embolism (12) in patients with HES. All these cases had high eosinophil counts, showing the relationship between the active disease and hypercoagulability state. These cases were treated with corticosteroids and anticoagulants with good clinical response. Different anticoagulants were used, including warfarin, rivaroxaban, and argatroban. Ventricular thrombosis or embolic event originating from ventricles may be another indication for anticoagulant therapy (1, 5).

Prophylactic administration of anticoagulants in HES is more controversial. Infusion of < 1000 units/hour of heparin didn`t prevent the formation of mural thrombosis in one study(5). There is no recommendation to start anticoagulants in the outpatient setting. However, we admitted our first case in the cardiac care unit with complete bed rest, so there was a concern for thrombosis formation due to prolonged immobility besides the hypercoagulability. We decided to initiate heparin infusion, but the initiation rate was above 1000 units/hour, activated partial thromboplastin time (aPTT) was checked frequently, and it was kept near the upper therapeutic limit. Although it was suggested that low molecular weight heparin (LMWH) is also a good prophylactic choice (5), we decided not to use it due to the unknown anticoagulation effect of LMWH in the HES due to lack of monitoring.

COVID-19 can also alter the coagulation status. There are reports on increased D-dimer levels in COVID-19 patients, which is related to a worse prognosis (13, 14). Fibrinogen level is also increased (13). Elevation of pro-inflammatory cytokines, especially interleukin-6, can result in elevated tissue factor expression (13, 14). Furthermore, the virus uses the angiotensin-converting enzyme 2 (ACE2) to enter cells. This results in downregulation of ACE2 and dominancy of pro-inflammatory actions of angiotensin II as a consequence, including more expression of tissue factor (14, 15). These changes can result in a hypercoagulability state and an increased risk of thrombotic complications. Our second case was admitted with a high eosinophil count, reflecting an active disease status. We believed that his concurrent COVID-19 disease resulted in mechanical valve thrombosis because both HES and COVID-19 are associated with the hypercoagulability state, and may have had additive effects. The patient`s INR was subtherapeutic on admission despite no change in his surveillance, diet, or drugs. Maybe this decrease was due to the enhancement of factor VII, which is activated by tissue factor. As it is mentioned above, both HES and COVID-19 can result in higher expression and activity of the tissue factor and, as a consequence, factor VII.

Conclusion

There are important considerations for therapeutic management of HES, including the time of surgery, selection of the prosthetic valve, and prophylactic or therapeutic anticoagulation. Furthermore, we must be aware that the COVID-19 pandemic can change the clinical course of HES. For instance, it can

exacerbate the myocardial injury and heart failure symptoms, as in our first patient, or increase the risk of thrombosis in prosthetic valves or native vessels due to the hypercoagulability state. Therefore, closer surveillance of patients is needed in the era of the COVID-19 pandemic.

Abbreviations

COVID-19: coronavirus disease 2019

HES: hypereosinophilic syndrome

hs-CTnI: high sensitive troponin I

LVEF: left ventricular ejection fraction

MS: mitral stenosis

MR: mitral regurgitation

NT-pro BNP: N terminal pro B type natriuretic peptide

TS: tricuspid stenosis

TR: tricuspid regurgitation

WBC: white blood cell

Declarations

Ethics approval and consent to participate

Informed consent was obtained from the patients for publication of this case report.

Consent for publication

Informed consent was obtained from the patients for publication of this case series.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article, and any other inquiry is available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FL and RS designed the study. MR performed the surgeries; MK, MF, SP, FS, ASa, and RP contributed to patients' care and management. FL and ASh collected and analyzed the data. ASh wrote the manuscript draft. All authors read, edited, and approved the final manuscript.

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Figures

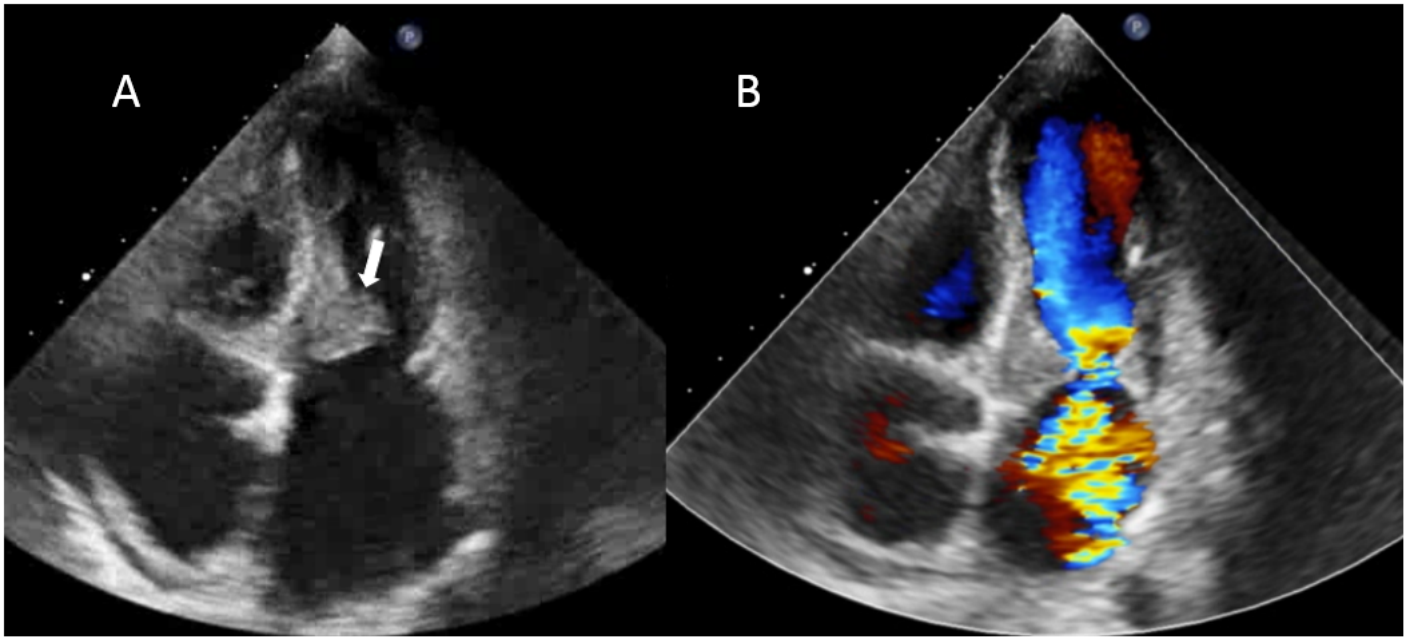

Figure 1

Apical 4-chamber view. An increased thickness in the ventricular side of mitral valve leaflets is seen (A, arrow), resulting in mass formation. Severe mitral regurgitation is also present (B).

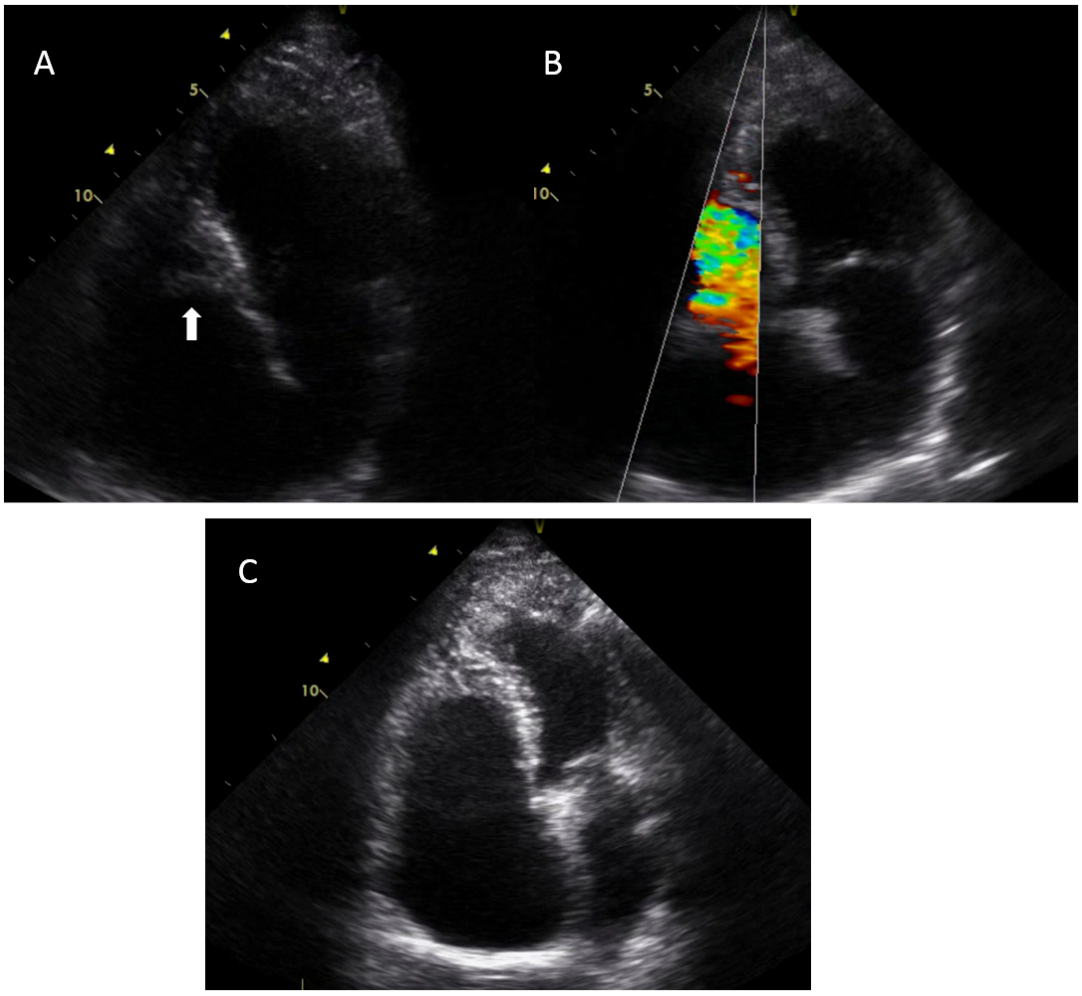

Figure 2

Apical 4-chamber view. Severe thickening of tricuspid valves with extension to the RV free wall is seen (A, arrow), resulting in an increased gradient and severe tricuspid stenosis (B). A follow-up echocardiogram two months later shows no evidence of tricuspid valve thickening and stenosis (C).

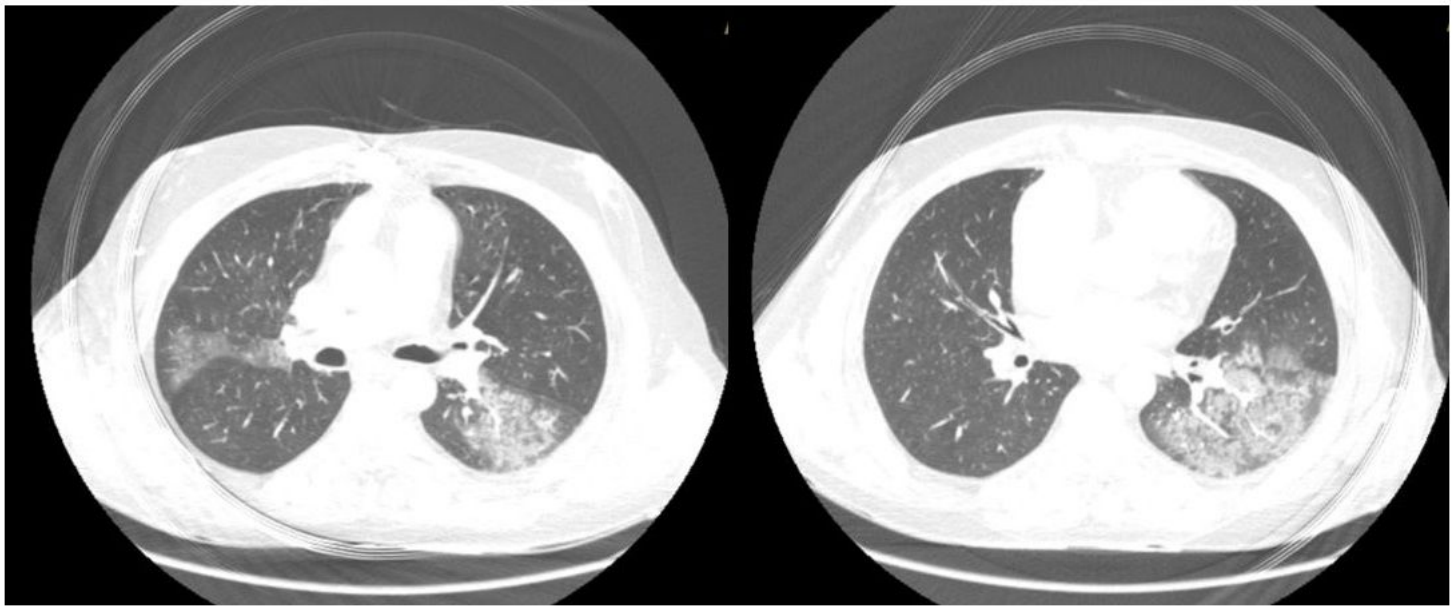

Figure 3

Chest CT scan shows ground glass opacities mostly in left lung in favor of COVID-19 infection.

Supplementary Files

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- VideoS1.wmv
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