Primary Cardiac Angiosarcoma With Pulmonary Metastasis in a Young Female: A Case Report and Review of Literature

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Case Report

Keywords: Angiosarcoma, Malignant Cardiac Tumor, Right Atrial Mass, Pulmonary Metastasis, COVID-19, Case Report

Posted Date: November 16th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2254385/v1

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Abstract

Background: Sarcomas are the most prevalent type of malignant primary cardiac tumor. Clinical presentation differs according to the size and location of the tumor and involvement of other structures.

Case presentation: In this article, we present a 38 years old lady as a case of primary cardiac angiosarcoma with a huge challenge in diagnosis and management of the disease. On the 4th of June 2020, she emergently presented to the hospital with the chief complaint of cough and tachypnea, diarrhea, and malaise, and a history of blunt chest trauma three weeks ago. Based on the presentation and transthoracic echocardiography which was compatible with cardiac tamponade, emergent pericardiocentesis was performed. The first imaging showed bilateral pleural effusion, pericardial effusion, and no significant parenchymal lung involvement, which was not compatible with rheumatologic diseases or COVID-19. Based on cardiac CT angiography and evidence of dye entrance to the peri-right atrial area, right atrial free wall rupture was suspected as the cause of the massive pericardial effusion. Following multidisciplinary consensus, she underwent cardiac surgery; in addition to the 3*3 cm right atrium free wall rupture repair, concomitant sampling from the lung nodules, lymph nodes, pericardium, and also the surrounding tissue of the right atrium ruptured defect was performed. Based on immunohistochemistry, the diagnosis was compatible with cardiac angiosarcoma with metastasis to the lung. Due to the advanced stage of the tumor, oncologists advised against chemotherapy or radiotherapy and she went through palliative care. Finally, after a 53-day ICU stay and due to right-sided heart failure, the patient unfortunately died.

Conclusion: COVID-19 pandemic has brought diagnostic challenges regarding differentiating SARS-CoV-2 infection from other diagnostic entities. On the other hand, due to the rarity and fatality of primary cardiac angiosarcomas, early diagnosis and possible management seem crucial for prolonged survival. Involving cardiac angiosarcoma in the initial differential diagnosis could warrant timely diagnosis and assessment of various therapies for cure or palliative care.

Background

Cardiac tumors consist of primary and secondary neoplasms (1). Although rare, angiosarcomas are the most prevalent type of malignant primary cardiac tumors (2, 3). Clinical presentation differs according to the size and location of the tumor and involvement of other structures (4). Angiosarcomas of the heart are mainly discovered in the right atrium (5). The most common symptoms, include dyspnea, fatigue, cough, signs of cardiac failure, chest pain. As highly aggressive tumors, cardiac angiosarcomas are known with a poor prognosis due to the high prevalence of distant metastases at the time of diagnosis. Diagnosis is of important concern because of its rarity and cytomorphological diversity. Practical tools guiding the diagnosis are transesophageal echocardiography (TEE), computed tomography (CT)-scan, magnetic resonance imaging (MRI), pericardial biopsy, etc. (6). Histologically, diagnosis appears mystifying due to similarities with benign tumors. Yet, the sinusoidal pattern seems pathognomonic. Moreover, endothelial markers such as CD-31, CD-34, FLI-1 may contribute to the diagnosis of
angiosarcoma (7, 8). Obstacles to treatment and low survival rate is at least partially related to not only delay in discovery of the disease, but also lack of response to different therapies; hence the need of a combination of multiple treatment modalities like resection, chemo-radio therapy, or finally, heart transplant. Hence, we present a case of primary cardiac angiosarcoma in a young woman with a huge challenge in diagnosing and treating the disease.

**Case Presentation**

The patient was a 38-year-old woman who presented on 4 June 2020 with a 3 weeks history of diarrhea, malaise, and occasional cough. Also, the patient mentioned a history of blunt chest trauma (her 6-year-old child jumped on her chest) almost 3 weeks earlier and the patient experienced severe chest pain at that moment. Her past medical history was unremarkable for systemic diseases and psychosocial history did not include using tobacco, alcohol, or illicit drugs. On first admission, her chief complaint was malaise, mild tachypnea, and right shoulder pain, and physical examination was remarkable for mild to moderate ascites and mild lower extremities edema. Hemodynamics were stable except for tachycardia. Due to the COVID-19 pandemic, she was mostly suspected of coronavirus infection. Hence, a chest CT-scan was performed, fluid accumulation around the heart was noticed in addition to bilateral pleural effusion (more prominent on the right side) (Chest CT-scan shown in additional file 1). The next day, echocardiography was done (LVEF = 50%, normal left ventricle (LV) and right ventricle (RV) size and function, swinging heart, normal valves, significant diastolic collapse of right atrium (RA) and RV, massive pericardial effusion), and because of the detected massive pericardial tamponade, the patient was urgently taken to cat lab for emergency middle pericardiocentesis. Drainage consisted of 500 milliliters bloody effusion, of which the specimen for cytology was unfortunately lost in the laboratory. Moreover, pigtail was inserted for the patient. Afterwards, the patient was transferred to the cardiac care unit (CCU) for further evaluation and management. Ibuprofen and colchicine were administered for her during CCU admission. After pericardial fluid removal, staying at CCU for one day, the patient's tachypnea did not resolve; nevertheless, the left-side pleural effusion was aggravated. At that point, bilateral thoracentesis was accomplished. Thoracentesis lessened the dyspnea just after a few hours and the pleural fluid specimen was exudative with unremarkable cytology. Considering diagnostic workups, all rheumatologic and immunologic tests were negative, COVID-19 polymerase chain reaction (PCR) and antibodies tests were undetectable, routine blood tests were normal, tumor Markers (CEA, CA 19 – 9, CA 15 – 3, CA 125) and ESR were normal, with a mildly increased CRP. Also, chest CT-angiography (ruling out pulmonary thromboembolism (PTE)) was normal, and abdominal-pelvic ultrasonography and CT-scan did not show any abnormalities related to malignancies. Last chest X-Ray was normal after bilateral thoracentesis (shown in additional file 2). The patient was discharged from CCU after 10 days with a prescription containing Valsartan and Metoprolol Succinate, along with previous medications, Aspirin, Ibuprofen, and Colchicine. At this time, she did not show any signs and symptoms except tachycardia (PR: 110–120 beats/min). Conservative approach was decided as the management plan.

Cardiac MRI was done on July 1st which demonstrated Normal LV size without left ventricular hypertrophy (LVH) and with mildly reduced systolic function (LVEF: 50%), anteroseptal and inferoseptal
hypokinesia, and an elongated mural thrombus along RA free wall which was external to RAA (maximum thickness: 15mm, minimum length: 35mm). The mural thrombus was strongly high water content with evidence of edema in the basal and mid inferoseptal segments and with mild pericardial effusion; based on MRI criteria, no obvious finding of myocardial edema or fibrosis was seen, moreover, according to cardiac magnetic resonance (CMR) tissue characterization criteria (Lake Louise) RA clot with evidence of septal edema (contusion?) and suspicious to a sealed rupture of RA free wall was noted. The next echocardiography (5th of July) was satisfactory and the heart seemed to be regenerated (LVEF = 50–55%, normal LV size and function, normal RV size and function, no pericardial effusion, and apparently no clot) and recommended re-evaluation 2 months later. Due to the fact that clot was not detected on echocardiography, anticoagulant was not administered for the patient. At this time, patient’s previous symptoms were improved, nevertheless, an occasional cough was still present along with tachycardia (PR: 100–120 beats/min). In addition, the follow-up chest X-Ray during the next two months (July and August) were unremarkable.

In September, cough frequency and quality were increased; general malaise was also present. Plus, a CBC test showed anemia (Hgb = 8.8) of which the reason could not be explained. chest X-Ray taken on September 16th revealed some features similar to COVID-19, therefore, a CT-scan was done on the same day (Fig. 1). The findings again showed probability of coronavirus infection or miliary TB, even though the patient’s clinic and oxygen saturation and COVID-19 PCR were not compatible with coronavirus infection. Interferon beta (3 doses) and dexamethasone (5 doses) were administered, yet the cough was not relieved.

On September 27th, echocardiography showed Normal LV size and mild systolic dysfunction (LVEF: 50%), global hypokinesia, no LVH, no LV clot, early diastolic septal abnormal motion in favor of septal bounce, normal RV size and mild systolic dysfunction (MPI: 0.65), Normal LA size (LAVI :12.5 cc/m2 ), normal RA size (RAVI :18cc/m2), haziness (31*12mm) adjacent to RA free wall, mild MR, normal IVC size with > 50% respiratory collapse, small pericardial effusion (anterior of RV: 4mm) with no RV collapse, and recommended re-evaluation 2 months later. Following consulting with a heart failure fellowship, the patient was advised to 3 months later follow-up. Because of continued cough, the patient was referred to a pulmonologist on October 7th and started taking inhaled medications. However, due to severe malaise, dyspnea on exertion, and cough, a chest CT was repeated on October 17, which showed bilateral lung involvement with a different pattern than the previous ones. Moreover, pericardial effusion was obvious again (Fig. 2). ??????? During the following days (October 19th ), due to acute worsening of dyspnea and weakness, the patient was re-admitted. She underwent an echocardiography and contrasted multidetector CT (MDCT). Echocardiography was performed (LVEF: 45–50%, normal LV size with mildly reduced LV systolic function, global hypokinesia, mild MR, normal RV size and systolic function, mild TR, mild PAH (PAP: 35 mmHg), significant transvalvular flow respiratory variation, severe pericardial effusion containing echogenic fibrinous strands and increased pericardial thickness; contrast agitated saline was injected but no bubble passage was detected). Contrast MDCT (Fig. 3) demonstrated infiltrative tumor arising from right atrium (RA) and defect in the wall of RA and sealed IV contrast. Large pericardial effusion was noted. Also, there were multiple pulmonary nodules in both lungs that had much more
aggressive pattern compared to the previous study which was suggestive of a tumor. Finally, with the diagnosis of cardiac tamponade due to RA rupture after expert consensus decision, the patient underwent open heart surgery (October 20th). At this timepoint, her Hemoglobin level was 6 g/dL. After midline sternotomy, the pericardium was seemed to have a significant inflammation and an active bleeding from visceral pericardium. There was a large perforation with size 30*30 mm in RA free wall. There was adhesion of pericardium to RA (site of healed perforation). Surgeon also reported diffuse small soft yellow nodular lesions in both lungs, which were scattered throughout the parenchyma of all lobes. Biopsies were taken from lung nodules, lymph nodes, pericardium and also surrounding tissue of the RA ruptured defect. The patient was successfully weaned off cardiopulmonary bypass. Afterwards, histopathologic and immunohistochemical investigation of lung nodules confirmed the diagnosis of poorly differentiated neoplasm suggestive of angiosarcoma positive for CD34, CD31, negative staining by PanCK, CAM5.2, SALL4, Calrtinin, MelanA, S100, Desmin, Bc12 and H-caldesmon. Histopathologic findings of pericardium and lymph nodes demonstrated only two reactive lymph nodes and fibrovascular tissue containing some organized thrombi and focal chronic inflammation. Due to failed extubating, tracheostomy was done after 9 days. While in ICU, lung involvement progressed, and bronchoscopy was done ruling out COVID-19 and opportunistic infections.

During ICU stay, although the surgeon seemed satisfied with the operation process, hemoglobin was still around 7–8 g/dL, and the patient required several transfusions. Due to the advanced stage of the tumor, oncologists advised against chemotherapy and radiotherapy and recommended palliative care. After 40 days staying at ICU, she developed lower extremities edema and ascites. The next echocardiography indicated RV failure. During the following days, the patient’s hemodynamics were unstable she was unfortunately expired on December 10.
### Table 1
Timetable of symptoms, diagnostic workups and interventions

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Signs /Symptoms /Work-up/Management</th>
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| June         | • Signs and symptoms: Diarrhea and cough, malaise, tachypnea, tachycardia  
              | • Chest CT (June 4): *pericardial and bilateral pleural effusion*  
              | • Echocardiography (June 5): *cardiac tamponade, massive pericardial effusion*  
              | • Pericardiocentesis: 500 ml bloody *fluid drainage*  
              | • Bilateral thoracentesis  
              | • Chest X-Ray after thoracentesis (June 6): *Normal*  
              | • Chest CT-angiography: *Normal*  
              | • Abdominal-pelvic CT scan: *Normal*  
              | • Rheumatologic markers: *Negative*  
              | • Covid PCR: *Negative* |
| July         | • Signs and symptoms: tachycardia, cough  
              | • Echocardiography (July 1): *No significant pleural or pericardial effusion, no clot found*  
              | • Cardiac MR (July 5): elongated mural thrombus along RA free wall external into RAA (maximum thickness: 15mm, minimum length: 35mm) with mild pericardial effusion, no myocardial edema or fibrosis.  
              | • Chest X-Ray (July 25): *normal*  
              | • Rheumatologic markers: *Negative*  
              | • COVID-19 PCR: *Negative* |
| September    | • Signs and symptoms: Cough, malaise, tachycardia  
              | • Chest X-ray and chest CT (September 16): *suspicious of COVID-19*  
              | • Treatment with Interferon and dexamethasone  
              | • Echocardiography (September 27): *mild pericardial effusion*  
<pre><code>          | • Lab data: *anemia* |
</code></pre>
<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Signs /Symptoms /Work-up/Management</th>
</tr>
</thead>
</table>
| October     | • Signs and symptoms: Severe malaise, Dyspnea on exertion, tachycardia  
• Chest CT (October 17): *bilateral lung involvement with pericardial effusion*  
• Echocardiography (October 19): *massive loculated pericardial effusion*  
• Cardiac spiral CT-scan with contrast (October 20): *Suspicious tumoral lesion in the wall of RA with multiple tumoral lung lesions*  
• Surgery (October 20): *Full sternotomy, pericardiectomy, Repair of RA rupture (4cm)*  
• Pathology and IHC report: *metastatic angiosarcoma*  
• Post-surgery ICU stay (53 days): *Mechanical Ventilation, Tracheostomy, several transfusions, Palliative care* |
| November    | • RV failure, death |

**Discussion And Conclusion**

Herein, we reported a case of cardiac angiosarcoma with the chief complaint of cough, diarrhea, and a history of chest trauma 3 weeks before, whose chest imaging was normal and not compatible with rheumatologic diseases or COVID-19; and in the end, RA rupture occurred with the pathologic findings leading to the final diagnosis. Diagnosis of morbidities during the COVID-19 pandemic is of significant importance, especially those which share common clinical and/or paraclinical features with coronavirus infection. COVID-19 pandemic has brought diagnostic challenges regarding differentiating SARS-CoV-2 infection from other diagnostic entities. There are several cases reported in the literature describing complexities that hinder the diagnosis and management of many other infectious and non-infectious conditions in the COVID-19 pandemic era (9–12); among these is a case of cardiac liposarcoma recurrence with symptoms of dyspnea, palpitation, fever, and sore throat (10). Unfortunately, many cases of cardiac angiosarcoma are not timely diagnosed despite multimodality workups such as echocardiography, chest CT scan, HRCT, and biopsy, due to a broad spectrum of differential diagnoses such as benign tumors, viral, mycobacterial, or rheumatologic diseases being investigated (13).

There are reports of cardiac angiosarcoma in literature, most of which involved the right atrium with metastasis to the lung. The most prevalent symptoms were dyspnea, chest pain, tachycardia, pleural and pericardial effusion (7, 14–19). There were also cases presented with left atrium mass (20, 21), ascites (16), SVC involvement (8, 19, 22, 23), valvular complications (18, 20), tamponade and shock (24, 25), involvement of coronary vessels (26, 27), or heart rhythm abnormalities (20). In our patient, a rupture in the atrial wall was discovered which was assumed to be the underlying cause for her symptoms. There are similar cases reported in the literature in whom perforations in the cardiac chambers' walls were encountered (28). Reviewing the available literature regarding management strategies, some patients underwent surgery, along with radiotherapy and chemotherapy with regimens containing various drugs
such as Ifosfamide, Epirubicin, and Taxanes. Most of these treatments failed to control the disease and prolong survival (7, 8, 17, 19, 29–31). A case report has proposed complete resection of the tumor and aggressive reconstruction of the involved structures as a successful strategy to prolong patient survival for up to two years (21).

Among sarcomas, 40 percent are angiosarcomas which are composed of malignant cells forming vascular channels. Angiosarcomas arise predominantly in the right atrium (32). Sarcomas tend to proliferate rapidly and cause death via the widespread infiltration of the myocardium, blood flow obstruction, and even invasion and metastasis. Men are at least two times more likely than women to be diagnosed with primary cardiac angiosarcomas, knowing that it mostly affects the young. However, a multicenter cohort demonstrated no difference in 30-day and late mortality between males and females (3).

Echocardiography remains the major diagnostic tool with high sensitivity for cardiac mass detection and evaluation, identifying size, shape, location, attachment, and mobility of the mass. Meanwhile, a CT scan offers better recognition of the tumor anatomy and systemic metastasis. Cardiac MRI is a strategy to understand soft tissue and myocardium and to discern tumors from thrombi (33). Another practical approach is pericardiocentesis and tissue biopsy, keeping in mind that endomyocardial biopsy is a poor diagnostic tool (34). All of these strategies were performed as part of our diagnostic approaches. Majority of reported cases in the literature have performed chest CT-scan, TTE, and cardiac MRI for diagnosis. Histopathological studies following surgical (30, 35) or even core-needle biopsy (23) have been utilized to diagnose angiosarcoma. Besides, recently positron emission tomography-CT (PET/CT) scan using fluorodeoxyglucose (FDG) have helped further characterization of the tumor and systemic evaluation of the patient (30, 31, 36–39).

Surgery is a particular therapy, especially in the case of localized disease. Wide resection is considered a principal treatment approach as it not only enables a definite histological diagnosis, but also alleviates symptoms caused by cardiac output obstruction. Some of the tumors were reported presumably inoperable due to multiple metastases or adhesion to the RV (23, 29, 39). Alternative strategies such as orthotopic heart transplantation in the patients with high-grade angiosarcomas, especially in young patients for whom we do not have other options, have also been explored (34). Chemotherapy, both neoadjuvant and adjuvant, is sometimes utilized to augment the poor outcome of resection alone (22, 29–31, 35), or in cases which resection of the tumor is no feasible, long courses of chemotherapy with different agents might be helpful. For example, one center started chemotherapy with paclitaxel and bevacizumab for almost one year, which led to a decrease in tumor size, and finally pazobanib, ifosfamide, and doxorubicin were administered due to detection of pulmonary and liver metastasis (39). A recent case presentation also involved using immunotherapy with pembrolizumab as part of management of primary cardiac angiosarcoma with pulmonary nodules and bone destruction (31). Although not so common, radiation therapy has also been used in angiosarcomas, mainly in the setting of metastases (22, 30, 31, 40). A young boy with angiosarcoma was managed using MR-guided radiotherapy and demonstrated acceptable tolerance and a stable disease for two months (41).
According to the fact that treatments for angiosarcomas are not standardized, a combination of aforementioned modalities might be favored (42). However, it is noteworthy that the primary site of the tumor and stage at the time of diagnosis influences the plan of therapy (34).

Most patients end up with recurrent disease and death even in case of complete tumor resection (43, 44). The median survival is considered to be 6–12 months (45); however, there are reports of cases with longer survival rates and also better prognosis in cases with complete surgical resection or lack of metastasis on presentation (22, 46, 47). On the other hand, with heart transplantation, the mean survival rate could be about 12 months. In general, no established prognostic factors have been recognized in these patients.

Angiosarcomas are sometimes asymptomatic, yet, may present with constitutional symptoms such as shortness of breath, fatigue due to anemia, malaise, weight loss, with dyspnea being the most common complaint. This nonspecific symptomatology and rarity of the disease leads to difficulties in diagnosis, even though more characteristic symptoms may develop later as the disease progresses related to involvement of cardiac wall, neighboring structures, infiltration, and also disease extension and metastases (31, 34). In more advanced angiosarcomas, myocardial wall necrosis and rupture, pericardial involvement and effusion, and cardiac tamponade, right-sided congestive heart failure, and systemic symptoms due to blood flow obstruction may manifest in the course of the disease (29, 34). Likewise, our patient was first suspected of being infected with SARS-CoV-2 despite negative COVID-19 PCR, but later during the follow-up, symptoms did not still comply with the viral disease until her condition was emergent, leading to the following interventions and diagnoses. Finally, despite surgery, the patient unfortunately suffered invasive tumor complications that put an end to her life.

In conclusion, due to rarity and fatality of primary cardiac angiosarcomas, early diagnosis and possible management seem crucial for prolonged survival. Involving cardiac angiosarcoma in the initial differential diagnosis can warrant timely diagnosis and assessment of various therapies for cure or palliative care.

Abbreviations
<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CBC</td>
<td>complete blood count</td>
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<tr>
<td>CCU</td>
<td>cardiac care unit</td>
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<td>CEA</td>
<td>carcinoembryonic antigen</td>
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<td>CMR</td>
<td>cardiac magnetic resonance</td>
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<td>COVID-19</td>
<td>coronavirus disease 2019</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>CT-scan</td>
<td>computed tomography-scan</td>
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<td>FDG</td>
<td>fluorodeoxyglucose</td>
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<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<td>ICU</td>
<td>intensive care unit</td>
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<td>IHC</td>
<td>immuno-histochemistry</td>
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<td>LA</td>
<td>left atrium</td>
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<td>LAVI</td>
<td>left atrium volume index</td>
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<td>LV</td>
<td>left ventricle</td>
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<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<td>MR</td>
<td>mitral valve regurgitation</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>MDCT</td>
<td>multidetector computed tomography</td>
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<td>PAH</td>
<td>pulmonary artery hypertension</td>
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<td>PAP</td>
<td>pulmonary artery pressure</td>
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<td>PET</td>
<td>positron-emission tomography</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PR</td>
<td>pulse rate</td>
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<td>PTE</td>
<td>pulmonary thromboembolism</td>
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<td>RA</td>
<td>right atrium</td>
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<td>RAA</td>
<td>right aortic arch</td>
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<td>RAVI</td>
<td>right atrium volume index</td>
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<td>RV</td>
<td>right ventricle</td>
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Declarations

Ethics approval and consent to participate

Based on the TUMS Research Ethics Committee in Imam Khomeini Hospital Complex, the patient was aware that her medical information would be shared for the purpose of scientific publication and presentation.

Consent for publication

Written informed consent for publication of the clinical details and clinical images was obtained from patient’s family.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional files and also would be available anytime through requesting from the corresponding authors.

Funding

The authors declare that they have no source of funding.

Competing interests

The authors declare that they have no competing interests.

Author’s contributions

N Kordjazy wrote and edited the manuscript including the tables and figures, P Taheri collected all data and critically revised the manuscript, R Parkhideh edited the manuscript, A Nakhaee and B Shahrami helped in editing the manuscript, R Sattarzadeh performed diagnostic evaluations such as echocardiography and contributed to interpretation of data, M Foroumandi, A Najafi, and A Sadat Naseri helped in the ICU care of the patient and interpreting patient’s data, M Mojtabahedzadeh provided ICU care for the patient.

All authors have read and approved the manuscript.

Acknowledgements
The authors thank Dr. Shahrokh Karbalaei Saleh for his help and support in patient management and his comments for case presentation.

References


Figures
Figure 1

Chest X-ray and HR-CT-scan of lung: Bilateral ground glass opacities in parenchymal and subpleural area with no space occupying lesion or pleural effusion.
Figure 2

Chest X-ray and CT-scan: Nodular pattern
Figure 3

Spiral CT-scan of the cardiac with and without contrast

Supplementary Files

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- additionalfile2.jpg