Case report

Atypical rapid onset Scleroderma Renal Crisis (SRC) complicated with diffuse alveolar hemorrhage and pleuro-pericardial effusions in a patient with recently diagnosed breast cancer and a positive anti-RNA polymerase III Ab: A case report

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1. Background

Systemic sclerosis (SSc) is a chronic disorder of connective tissues characterized by inflammation, fibrosis, and degenerative changes in the blood vessels, skin, and visceral organs, notably the gastrointestinal tract, lung, heart, and kidney. Scleroderma Renal Crisis is well known as one of the life-threatening complications of SSc and is recognized by malignant hypertension, acute kidney injury (AKI), thrombocytopenia and microangiopathic hemolytic anemia (MAHA) [1]. Pulmonary-Renal Syndrome (PRS) is a combination of severe and acute lung disease, such as Diffuse Alveolar Hemorrhage (DAH), and acute renal failure in patient with SSc. Pulmonary-Renal Syndrome is a rare but severe complication of SSc with poor prognosis and high mortality rate [2-6].

2. Case presentation

A 66-year-old female with history of stage IIB right breast cancer, diagnosed 5 months prior to this admission, had bilateral mastectomy and lymph node resection. She refused chemotherapy and did not tolerate hormonal therapy. She presented with a 1-month history of shortness of breath. On physical examination, she had normal vital signs, mild swelling of the right upper and both lower extremities, and no significant skin changes. CT scan of the chest with IV contrast revealed bilateral moderate pleural effusion and pericardial effusion (Fig. 1), which was managed by thoracentesis. Analysis of the pleural fluid revealed bilateral moderate pleural effusion and pericardial effusion (Fig. 2). Consequently, cardiothoracic surgery was consulted and performed a pericardial window. Pericardial fluid analysis revealed negative culture and cytology, pericardial tissue pathology was negative for cancer, excluding infection and malignancy as a cause of her symptoms. The patient was subsequently discharged home.

She returned 25 days later with worsening SOB. At this time she had notable skin changes consistent with scleroderma skin changes. Work up revealed recurrence of bilateral pleural effusion and pericardial effusion. Thoracentesis was repeated which revealed xerostomia with negative culture and cytology. Further laboratory workup revealed increase in creatinine from 0.8 \( \mu \text{mol/L} \) at baseline to 2.6 \( \mu \text{mol/L} \),...
significantly elevated RNA polymerase III IgG Ab at 159.8, positive ANA: 1:1280 in speckled pattern, LDH 438 U/L; D-dimer 7.1 μg/mL; INR 1.02 and PTT 11.1 sec, fibrinogen 238 g/L, reticulocyte count 6.48, hemoglobin 7.2 g/dl, platelet 219 × 10⁹/L, peripheral Smear; ++ Schistocyte. Extensive workup for SLE, RA, ANCA vasculitis, anti-GBM disease, HUS, sjögren’s syndrome, HIV, HBV, HCV, were negative. Subsequently the patient underwent renal biopsy that showed Thrombotic Microangiopathy (TMA) (Figs. 3–8). Renal biopsy was complicated with right subscapular and retroperitoneal hematoma for which she had successful arterial embolization by our Interventional radiology group was consulted and did an embolization of the right renal artery. Following the procedure, she failed extubation and was transferred to the ICU. On day 18 of her hospital stay, she was noticed to have blood tinged sputum. Fiberoptic Bronchoscopy was performed with BAL consistent with diffuse alveolar hemorrhage (DAH).

The patient was initially empirically started on high dose steroid for possible autoimmune disease, however after her renal biopsy, a diagnosis of systemic sclerosis was made and her steroid was tapered and started on oral captopril 6.125 mg twice daily that slowly increased to 25 mg three times daily and along with plasmapheresis. After developing DAH, she was started on IV cyclophosphamide. The patient did not respond to this treatment and so Eculizumab was started. Despite the aggressive management the patient passed away.

3. Discussion

Scleroderma or systemic sclerosis (SSc) is a heterogeneous disorder characterized by endothelial dysfunction, dysregulation of fibroblasts resulting in excessive production of collagen and profound abnormalities of the immune system. These changes cause progressive fibrosis of the skin and internal organs, system failure, and death [7]. Pulmonary-Renal Syndrome characterized by diffuse alveolar hemorrhage and acute renal failure is a rare but devastating complication with high mortality that can be associated with systemic sclerosis.

Systemic sclerosis with PRS can be categorized into three subsets: scleroderma PRS with thrombotic microangiopathy (TMA), scleroderma PRS with small vessel vasculitis, and Good pasture-like
syndrome induced by high-dose d-penicillamine (DPC) therapy in scleroderma patients [2]. Our patient had scleroderma PRS with thrombotic microangiopathy (TMA) that was shown on renal biopsy.

There are emerging evidence from recent case series and epidemiological studies that suggest an increased risk of SSc in association with various malignancies. In a case series by Shah et al., they found that patients with anti-RNA polymerase III (anti-RNAP) antibody developed SSc within 2 years of cancer onset in a cohort of 23 patients [8]. Airò et al. also reported a clustering of cancers with SSc onset in a small sample of patients with anti-RNAP antibodies [9]. A recent large single-center cohort study in the UK by Moi zincadeh, Pia, et al. found that breast cancers were temporally associated with the onset of SSc among patients with anti-RNAP, and SSc patients with anti-RNAP had a two-fold increased hazard ratio for cancers compared to patients with ACAs (P < 0.0001) [10]. In our case, the patient initially was diagnosed with stage IIB right breast cancer and then six months later was diagnosed with SSc and anti-RNAP was significantly elevated at 159.8.

It is rare for SSc to present with pericardial effusion as a first sign. It is not uncommon to have small pericardial effusions in SSc, and pericarditis is a frequent postmortem finding [11]. Large hemodynamically significant pericardial effusions with cardiac tamponade are rare and have a poor outcome [11]. Our case presented with SOB and found to have pericardial and bilateral pleural effusions. These signs and symptoms happened before the patient developed skin manifestations, which caused us to believe at the beginning that they were attributed to her history of breast cancer. However, after extensive workup, including negative cytology on pleural fluid analysis, and especially with development of SSc skin manifestations during the second hospital...
admission, it was proposed to be caused most probably by her atypical rapid onset SSc.

According to the subset of PRS, therapeutic strategies may contain common and specific approaches. In general, if the patient is taking DPC [write in full], it should be immediately withdrawn and accelerated hypertension or hypertensive SRC should be treated with ACE-I. ACE-I is also recommended for the management of normotensive SRC even if in a smaller dosage [2,6].

Other treatment modalities include plasma exchange, corticosteroids, and immunosuppressants. The most important component of treatment is plasma exchange, and may be indicated for all patients with suspected TMA [12], and may be an effective measure for the treatment of scleroderma PRS with TMA.

There are suggestions that cyclophosphamide may be beneficial for the treatment of interstitial lung disease associated with SSc. Although the efficacy of this drug for the treatment of PRS in SSc is uncertain, cyclophosphamide can be an option to treat PRS with vasculitis and to obtain immunosuppressive effects, in place of high-dose corticosteroids in PRS with TMA [6].

It has been reported that early administration of C5 inhibitor Eculizumab may have therapeutic potential in patients with life-threatening SRC refractory to conventional treatment with corticosteroids, plasmapheresis, and renin–angiotensin pathway inhibitors [13].

Our patient was started on Prednisone 40mg on day 6 that was increased to 60 mg daily on day 11 for suspected autoimmune disease. Patient was then switched to IV methylprednisolone, and started on captopril and plasmapheresis after diagnosis of SRC with TMA. After developing DAH, she was started on IV Cyclophosphamide. The patient did not respond to the treatment and was started on Eculizumab as a last resort. Despite the aggressive management the patient passed away.

4. Conclusion

High index of suspicion is needed for early recognition of this potential complication in patients with systemic diagnosis presenting with acute respiratory distress. Starting appropriate treatment in timely fashion is essential to avoid complication and achieve possible remission. Further studies are needed to elucidate the pathogenesis of this disorder and to explore the effective therapeutic measures as well as to evaluate the biological link between anti-RNAP antibodies and malignancy in SSc.

Declarations

Funding

Not applicable.

Availability of data and materials

All data are available in the manuscript.

Authors’ contributions

Obadah Aqtash, MD, Ibrahim Shahoub participated in data collection and interpretation, and drafted the initial manuscript. Emhemmid Karem and Hazim Bukamur participated in data collection and processing and critically revised and written the manuscript. Fuad Zeid supervised and helped writing the case report. Dr. Iheanyichukwu Ogu provided the pathology slides and insight about the case and critically revised all written the manuscript. All authors read and approved the final version of the manuscript.

Competing interests

Hazim Bukamur, Obadah Aqtash, Ibrahim Shahoub, Emhemmid Karem, Iheanyichukwu Ogu and Fuad Zeid have no competing interests to disclose related to the contents of the manuscript.

Consent for publication

Not applicable.

No consent needed as this is a case report without any patient identifiers.

Ethics approval and consent to participate

Not applicable.

No ethics approval nor consent is needed as this is a case report without any patient identifiers.
Acknowledgements

The authors acknowledge and thank the department of Nephrology, Pulmonary and Oncology at Marshall university for their help and contribution.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.rmcr.2018.08.010.

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