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A Case of Undifferentiated Connective Tissue Disease Presenting as Anemic Heart Failure

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Abstract: ***UCTD is a connective tissue disorder, which does not meet the diagnostic criteria for a single disease. It is an autoimmune connective tissue disorder marked by serological autoimmune manifestations; UCTD can develop into a systemic autoimmune disease in 30% of patients as more diagnostic criteria are progressively met. The pathogenesis of UCTD is likely a combination of the autoimmune - mediated pathogenesis seen in single disease states. Here is the case of a 69 year old female who has a history of recurrent blood transfusion due to anaemia presented with chest pain, breathlessness and severe pallor. Last blood transfusion was one month back when the patient had been admitted with a haemoglobin of 3.5 and discharged with a haemoglobin of 8.5 post multiple whole blood transfusions. On lab investigations, Patient had a haemoglobin of 4 on admission and a retic count of 1.2% with low iron levels suggestive of iron deficiency anaemia but it could not explain the recurrent and rapid fall in Hb for which we did various investigations to rule out other types of anaemia and found ANA to be positive. On ANA profiling Centromere B was found to be positive suggestive of Systemic sclerosis or CREST syndrome but the patient did not meet the dia gnostic criteria for either hence leading to the diagnosis of Undifferentiated connective tissue disease. Patient was managed with Hydroxychloroquine and Steroid and advised a Rheumatologist Opinion.***

Keywords: Undifferentiated Connective Tissue Disease; Connective tissue disease; Anaemia of chronic disease

1. Introduction

Undifferentiated connective tissue disease is a clinical entity defined as serological and clinical manifestations of systemic autoimmune disease. However, not fulfilling any criteria of defined connective tissue disease such as systemic lupus erythematosus, mixed connective tissue disease, Sjögren syndrome, systemic sclerosis, polymyositis, dermatomyositis, or rheumatoid arthritis. [1]

A small percentage of patients presenting with an undifferentiated profile will develop during the first year follow up of a full blown CTD, however an average of 75% will maintain an undifferentiated clinical course. These patients may be defined as having a stable undifferentiated connective tissue diseases (UCTD). [2]

2. Case History

In this case. a 69 - year - old female, known case of Diabetes Mellitus and Hypertension since the last 15 years presented with a complaint of chest pain and breathlessness along with generalised weakness and lethargy
since the last 2 days, prompting a comprehensive investigation.

Patient gave a history of multiple blood transfusions in the past for which she was admitted 3 times in the past 1 year, the latest one month back during which after multiple blood transfusions she was discharged with a haemoglobin of 8 mg/dl and on iron supplements.

There was no history of hematemesis, Malena, Hematochezia or active blood less from any site, joint pain.

There was no family history of recurrent anaemia or any haematological conditions.

Clinical Examination:

On clinical examination, Patient was in a febrile condition and exhibited an increase in respiratory rate with a RR of 28/min and tachycardia of 122 beats per minute with a blood pressure of 94/68mmHg with SpO2 levels maintained at 98%.

There was severe pallor visible with bilateral pitting type of pedal edema with no clubbing, cyanosis, lymphadenopathy or icterus.

Patient was conscious, oriented to time place and person and following commands and had bilateral lower zone basal crepitations heard on auscultation of the lungs.

Laboratory Investigations:
Upon admission, the patient had a haemoglobin level of 4 mg/dl, accompanied by low iron levels and a reticulocyte count of 1.2%, with peripheral smear suggestion of hypochromic microcytic cells intermixed with normocytic normochromic cells indicative of iron deficiency anaemia. The recurrent and rapid decline in haemoglobin warranted a thorough exploration of potential causes. Various tests were conducted to rule out different types of anaemia, B12 levels were normal and Stool for occult blood was negative. The laboratory results showed an increased level of inflammatory parameters (erythrocyte sedimentation rate: 120 mm; C - reactive protein: >4.8 mg/dl.

This prompted us to do an ANA by IF which came out to be positive. Further analysis of ANA profiling identified Centromere B positivity, suggesting a potential link to Systemic Sclerosis or CREST syndrome.

	Day 1	Day 3	Day 7	Day 10
Hb	4	6.7	5.7	7.5
TC	9240	10590	10460	8800
RBC	1.99	3.48	2.56	3.24
APC	3.18	3.23	3.09	2.95

Rft: within normal limits
Lft: within normal limits
USG APK: Normal
2D ECHO: EF 45 percent
Mild LV Dysfunction
Moderate MR, Trivial TR
Stool for Occult blood - Negative
Urine routine microscopy - Normal
S. Iron: 32 mcg/dl
TIBC: 347 mcg/dl
UIBC: 315 mcg/dl
S. LDH: 257 U/L
CPK total: 37
Calcium: 8.3 mg/dl
Magnesium: 1.68 mEq/L
TSH: 1.9801 mU/L
Total protein: 6.6 g/dL
Albumin: 4.0 g/dL

3. Discussion

As the patient's ANA was positive and further centromere B was positive it directed to a diagnosis of Scleroderma or CREST syndrome. However, the patient did not meet the specific diagnostic criteria for either condition leading to a diagnosis of UCTD.

Undifferentiated connective tissue disease (UCTD) is a disorder characterised by the presence of clinical manifestations and laboratory evidence of systemic autoimmune disease, but failure to meet the criteria for any of the defined connective - tissue diseases (CTDs). [3] [4]

Clinical Signs and Symptoms:
Up to 90% of undifferentiated connective tissue disease cases occur in females, especially those between 32 and 44 years old, and the majority of these cases do not progress into a full - blown connective tissue disease. [5]

Aforementioned, symptoms may bee similar to any other connective tissue disease due to which the presentation can vary widely among patients.

However, some symptoms can be common for example, arthralgia can be present in up to 86% of patients; various skin lesions, including livedo, purpura, acrocyanosis, telangiectasias, and urticaria, can also be common (37%). Other common symptoms include the Raynaud phenomenon (33%), sicca symptoms (30%), mucocutaneous symptoms, such as oral ulcers (23%), and arthritis (22%), fever (15%), and thyroid disease (7%). [6] [7]

Undifferentiated connective tissue disease may have a mild clinical course. It usually doesn't involve major organ damages.

With this disease, the physical findings can be localised or diffuse, and it is best illustrated by organ systems, as the following:

- Skin - Sclerodactyly, calcinosis, discoid rash, erythema nodosum, periungual erythema, heliotrope rash, dilated or irregular nail fold capillaries, or subcutaneous nodules.
- Eyes – Iritis, uveitis, scleral - episcleral disease, or conjunctivitis.
- Lungs - Rales, pleural effusion, wheezing, or pleural rub
- Heart - Cardiomegaly, heart murmur, pericardial rub, irregular heartbeat, dependent edema, or irregular P2 heart sound.
- Gastrointestinal – Splenomegaly, abdominal tenderness, or hepatomegaly.
- Genitalia – Rashes, abnormal discharge, or ulcerations.
- Muscles – Proximal muscle weakness, muscle tenderness, tendon friction rubs, or muscle atrophy. [7] [8]

Diagnostic Evaluation:
Positive serological markers are considered essential in the diagnostic criteria for undifferentiated connective tissue disease, so the laboratory measures are beneficial in diagnosis, especially anti - Ro/SSA and anti - U1 - RNP. Other tests that are helpful in diagnosis include routine screening tests, which include: complete blood count, C - reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine, urinalysis with microscopic analysis, rheumatoid factor (RF), and antinuclear antibodies (ANA). [6]

In imaging studies, chest radiography and Computed tomography of the chest is needed ito rule out interstitial lung disease. Additionally, ultrasonography of the salivary glands can also be used to differentiate between undifferentiated connective tissue disease and Sjögren syndrome.

Other tests that may prove to be helpful: Pulmonary function tests, including lung volumes, spirometry, help in diagnosing interstitial lung disease. When patients have cardiac symptoms, electrocardiography and ECHO is useful in the detection of ischemic changes, infarction or low ejection fraction. The Schirmer test can also be used in patients with dry eyes for Sjogren syndrome.

Management
Undifferentiated Connective Tissue Disease usually has a mild clinical course and can be managed primarily as an outpatient. Many drugs can be used, including non – steroidal anti - inflammatory drugs, corticosteroids, calcium channel blockers, and antimalarial drugs such as hydroxychloroquine.

The management strategy implemented for this patient was focused on the administration of Hydroxychloroquine and Steroids, aiming to alleviate symptoms and potentially modify the course of the disease.

Tab HCQ (300mg) 0 - 0 - 1 and Tab Prednisolone (10mg) 1 - 0 – 0 was started and patients anaemia was gradually corrected with blood transfusion for immediate alleviation of symptoms. No further fall in Haemoglobin was noted in subsequent followups.

Furthermore, the patient was advised to seek the opinion of a Rheumatologist, emphasising the multidisciplinary approach required for comprehensive care.

Differential Diagnosis:
Undifferentiated Connective Tissue Disease is a diagnosis of exclusion, the diagnosis of this disease should not be confirmed until an extensive workup has been done. Other connective tissue diseases must be excluded while evaluating any patient presenting with features of this disease.

- Dermatomyositis
- Antiphospholipid syndrome
- Fibromyalgia
- Linear scleroderma and regional fibrosis
- Systemic lupus erythematosus (SLE)
- Mixed connective tissue disease (MCTD)
- Raynaud phenomenon
- Polymyositis
- Sjögren syndrom
- Systemic sclerosis
- Rheumatoid arthritis (RA)

4. Conclusion

This case underscores the complexity of UCTD, illustrating the intricate interplay between autoimmune- mediated pathogenesis and the challenges in reaching a definitive diagnosis. It emphasizes the importance of a nuanced clinical approach, considering both serological autoimmune manifestations and evolving diagnostic criteria, to effectively manage and treat patients with undifferentiated connective tissue disorders.

Ethical clearance: Patient's informed consent was obtained for the clinical information, details of investigations and radiological findings to be reported in the journal.

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Conflict of Interest: Nil

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