Journal of Community Hospital Internal Medicine Perspectives

Volume 14 | Issue 5 Article 16

2024

Admitted with epistaxis, discharged on immunosuppressants! - An Unusual Presentation of Mixed Connective Tissue Disease

Anne C Laird
Georgetown University School of Medicine, Washington, DC

Basem Al Achras
MedStar Health, Baltimore, MD, basemalachras1992@gmail.com

Recommended Citation

Laird, Anne C and Achras, Basem Al (2024) "Admitted with epistaxis, discharged on immunosuppressants! - An Unusual Presentation of Mixed Connective Tissue Disease," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 14: Iss. 5, Article 16.
DOI: 10.55729/2000-9666.1383
Available at: https://scholarlycommons.gbmc.org/jchimp/vol14/iss5/16

CASE REPORT

Admitted With Epistaxis, Discharged on Immunosuppressants! - An Unusual Presentation of Mixed Connective Tissue Disease

Anne C. Laird [a], Basem Al Achras [b,*]

[a] Georgetown University School of Medicine, Washington, DC, USA
[b] MedStar Health, Baltimore, MD, USA

Abstract

Mixed Connective Tissue Disease (MCTD) is a complex disease that is a combination of several other clinical conditions, including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis/dermatomyositis (PM/DM).

What makes MCTD challenging is the fact that there are no current management guidelines. Instead, treatment is usually chosen based on organ involvement using SLE, SSc, and PM/DM guidelines.

In this paper, we will discuss an unusual presentation of MCTD, the workup that led to the diagnosis, the immunological profile, and the management plan for this rare disease.

Keywords: MCTD, Scleroderma, Scleroderma renal crisis

1. Background

Mixed Connective Tissue Disease (MCTD) was first described in 1972 by Sharp and colleagues.[1] It was characterized as a mix of clinical components of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis/dermatomyositis (PM/DM) in addition to the presence of U1RNP antibodies, which are antibodies directed against the ribonucleoprotein.

The most common presentations of MCTD include polyarthritis, Raynaud's phenomenon (RP), sclerodactyly, myositis, and esophageal dysmotility. Constitutional symptoms are common, including fever, fatigue, muscle and joint pain. More severe manifestations, including kidney, gastrointestinal, pulmonary, cardiovascular, and central nervous system disease, often develop and progress over time.[2]

MCTD has a wide range of clinical manifestations and no gold-standard diagnostic criteria, making it a difficult diagnosis. Few diagnostic criteria have been proposed in the literature, including the Sharp, Alarcon-Segovia, Kahn, and Kasukawa criteria.

Briefly, the Sharp criteria require the presence of anti-U1RNP antibodies, negative anti-smith antibodies, and 2 major clinical symptoms of pulmonary involvement, esophageal dysmotility, Raynaud syndrome, swollen hands, and or myositis. The Kasukawa criteria categorizes symptoms into disease categories with different symptoms corresponding to PM-like findings, SSc-like findings, or SLE-like symptoms, with a diagnosis hinging on positive findings in at least two of the three categories and positive anti-RNP antibodies. Finally, the Alarcón-Segovia and Kahn criteria rely more heavily on the presence of high titer anti-RNP and ANA antibodies corresponding to an Anti-RNP/ANA titer of $\geq$1:1000 and 1:2000, respectively, in addition to two or three of the classic clinical findings described above.[3]

Overall, the presence of at least three clinical manifestations from any of these proposed criteria and fulfilling the serological criteria is sufficient to make the diagnosis.

Received 6 February 2024; revised 14 May 2024; accepted 3 June 2024.
Available online 9 September 2024

* Corresponding author. 1211 S Eaton St, Unit 6021, Baltimore, MD 21224.
E-mail address: basemalachras1992@gmail.com (B. Al Achras).

https://doi.org/10.55729/2000-9666.1383

There are no current guidelines on the management of MCTD; instead, treatment is chosen based on symptoms and organ involvement. It usually depends on SLE, SSc, and PM/DM guidelines.

2. Objective

MCTD is a complex disease with a difficult diagnosis and challenging management due to the lack of specific guidelines. In this report, we would like to discuss an unusual presentation of MCTD, the diagnostic workup, the management plan, and the course of our patient's illness.

3. Case report

A 35-year-old female with no past medical history presented with recurrent epistaxis for three months. This patient also reported several months of fatigue, proximal muscle weakness, loss of appetite and weight, GERD symptoms, painful cyanosis of the fingers not necessarily associated with temperature, daily migraines, and episodic blurry vision in her left eye. She also developed a shingles rash two days before her presentation, which was still present. Physical exam was remarkable for telangiectasia around the lips, a systolic heart murmur, tight skin on the dorsal side of the hands bilaterally, 4/5 generalized muscle weakness without focal deficits, and a crusting, red rash on the right chest and neck that did not cross the midline, consistent with healing herpes zoster lesions. Vital signs were notable for hypertension of 183/133.

Laboratory workup showed hemolytic anemia with elevated lactate dehydrogenase and positive Coombs, hypocomplementemia, elevated brain natriuretic peptide, elevated troponin which was believed to be due to demand ischemia in the setting of hypertensive emergency, proteinuria, hyperproteinemia, elevated liver function tests, and mildly elevated creatine kinase (CK). The patient was admitted for hypertensive emergency. She was started on Captopril for a suspected scleroderma renal crisis.

Immunological workup showed high titer positive antinuclear antibody (ANA) of 1:1280 but negative dsDNA, anticentromere, anti-DNA topoisomerase I (SCL 70), and RNA polymerase III antibodies. Further workup showed positive anti-Ro/SSA, antiphospholipid antibodies (APS 7), and positive PL-7 antibodies (threonyl tRNA synthetase antibody), and positive smith/RNP IgG antibodies of 122 units which indicates strong positivity as per the laboratory reference.

High resolution CT scan of the chest showed interstitial lung disease (ILD) features, specifically, bilateral lower lobe predominant interlobular septal thickening, reticulation, and mild ground glass opacities (Image 1). Pulmonary function test (PFT) showed a restrictive pattern with reduced diffusion capacity (DLCO). A transthoracic echocardiogram (TTE) suggested pulmonary hypertension; therefore, right heart catheterization was performed and was normal at rest. However, after 2 min and 40 s of exercise, the patient was found to have mild pulmonary hypertension with mean pulmonary artery pressure of 22 mm Hg. Pulmonary capillary wedge pressure (PCWP) was normal both at rest and with exercise, and therefore, the patient was diagnosed with mild pulmonary hypertension WHO type 1.

A cardiac MRI showed no cardiac involvement, and a kidney biopsy was performed and showed focal segmental sclerosis, likely secondary to uncontrolled hypertension.

Our patient's blood pressure normalized with the administration of nifedipine and captopril. Her headaches, possibly due to severe hypertension, also resolved with acetaminophen and blood pressure control. She was ultimately diagnosed with Mixed Connective Tissue disease and was started on hydroxychloroquine and mycophenolate. Despite this treatment, myositis symptoms persisted, and CK continued to be elevated. Therefore, an intravenous immunoglobulin (IVIG) course was added with some improvement in energy levels, muscle pain and weakness, and joint stiffness.

She is now scheduled to begin rituximab in the coming months for further control. Our patient continues to follow up with rheumatology, cardiology, pulmonary, nephrology, and ophthalmology.

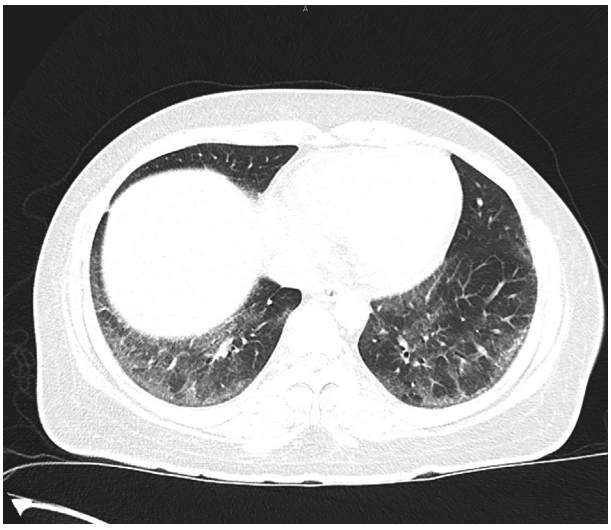

Image 1. High resolution CT scan of the chest showing bilateral lower lobe predominant interlobular septal thickening, reticulation, and mild ground glass opacities.

4. Discussion

Although this patient did not receive the highly specific U1 RNP antibody testing, she did have strongly positive anti-RNP antibodies. This, in the setting of myositis (PM-like findings), Raynaud's phenomenon, esophageal hypomotility, reduced diffusion capacity (SSc-like findings), and hemolytic anemia, lymphadenopathy (SLE-like findings), confirmed the diagnosis of MCTD specifically relying on Kasukawa criteria which is one of the major accepted criteria. Moreover, our case fulfills the Alarcón-Segovia criteria with strongly positive anti-RNP antibodies, high titer ANA antibodies of more than 1:1000, in addition to multiple clinical findings described above.[3]

Despite this patient's eventual diagnosis of MCTD, her presentation was hugely confounded by meeting criteria for several different rheumatological diseases, discussed below. Teasing out the different components of her overall disease process is tedious but clinically imperative, as the literature increasingly supports differing prognoses and medication responses based on the presence of specific antibodies and symptoms.

Whether MCTD is a distinct clinical entity, or an early presentation of other connective tissue diseases has long been debated. Although it is now widely accepted as a distinct diagnosis, it is easy to see why such discourse has existed. For example, in our case, at first blush, SSc seemed a likely diagnosis, as our patient met the criteria for scleroderma renal crisis (SRC) due to her severe hypertension, hemolytic anemia, proteinuria, and scleroderma skin features.[4] The patient's renal biopsy report showed significant microangiopathy, noting focal segmental glomerular sclerosis, arteriolosclerosis with an “onion-skinning” appearance, and mild arteriolar hyalinosis. Although SRC is characterized by prominent small vessel involvement, seemingly represented by the biopsy, this histology is technically non-specific and may be due to hypertension.[4]

Interestingly, antibodies to RNA polymerase III, which our patient did not have, are associated with a higher risk of progression to SRC for those with SSc. However, more recent studies have found that only half of patients who progress to SRC have anti-RNA polymerase III antibodies, so this certainly does not exclude the diagnosis.[5]

Further complicating our patient's presentation, she also met the diagnostic criteria for anti-synthetase syndrome: positive of anti-aminoacyl transfer RNA synthetase antibodies (PL-7 antibodies in our case) and clinical features such as ILD, myositis, and Raynaud's. Meeting these criteria may be more than just academically interesting, as it has been found that there is a higher prevalence and increased severity of interstitial lung disease in patients with anti-Ro/SSA positive anti-synthetase syndrome.[6] The biological cause of these patients having a higher frequency of lung involvement is unclear. The working hypothesis posits that a proteolytically sensitive conformation of histidyl-tRNA synthetase exists in the lung. Therefore, an immune response to this antigen may cause tissue damage.[7]

Lastly, patients with Ro-52 positivity, like our patient, were found to have a statistically significant increase in ILD, micro- or macroangiopathy, and relapses. This patient group was also noted to require more immunosuppressive medications.[8]

In conclusion, MCTD is a complex disease process with differing presentations; parsing out the unique clinical symptoms and the antibody profile is imperative in prognosis and management.

References

1. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease–an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med*. 1972 Feb;52(2):148–159. https://doi.org/10.1016/0002-9343(72)90064-2. PMID: 4621694.
2. Ortega-Hernandez OD, Shoenfeld Y. Mixed connective tissue disease: an overview of clinical manifestations, diagnosis and treatment. *Best Pract Res Clin Rheumatol*. 2012 Feb;26(1):61–72. https://doi.org/10.1016/j.berh.2012.01.009. PMID: 22424193.
3. John KJ, Sadiq M, George T, et al. Clinical and immunological profile of mixed connective tissue disease and a comparison of four diagnostic criteria. *Internet J Rheumatol*. 2020 Jan 29;2020:9692030. https://doi.org/10.1155/2020/9692030. PMID: 32411251; PMCID: PMC7204172.
4. Butler EA, Baron M, Fogo AB, et al. Generation of a core set of items to develop classification criteria for scleroderma renal crisis using consensus methodology. *Arthritis Rheumatol*. 2019 Jun;71(6):964–971. https://doi.org/10.1002/art.40809. Epub 2019 Apr 12. PMID: 30614663.
5. Nguyen B, Assassi S, Arnett FC, Mayes MD. Association of RNA polymerase III antibodies with scleroderma renal crisis. *J Rheumatol*. 2010 May;37(5):1068. https://doi.org/10.3899/jrheum.091048. author reply 1069. PMID: 20439528; PMCID: PMC2879023.
6. La Corte R, Lo Mo Naco A, Locaputo A, Dolzani F, Trotta F. In patients with antisynthetase syndrome the occurrence of anti-Ro/SSA antibodies causes a more severe interstitial lung disease. *Autoimmunity*. 2006 May;39(3):249–253. https://doi.org/10.1080/08916930600623791. PMID: 16769659.
7. Levine SM, Raben N, Xie D, et al. Novel conformation of histidyl-transfer RNA synthetase in the lung: the target tissue in Jo-1 autoantibody-associated myositis. *Arthritis Rheum*. 2007 Aug;56(8):2729–2739. https://doi.org/10.1002/art.22790. PMID: 17665459.
8. Decker P, Moulinet T, Lopez B, et al. Clinical significance of anti-Ro52 (TRIM21) antibodies in adult patients with connective tissue diseases. *Eur J Intern Med*. 2021 Sep;91:45–52. https://doi.org/10.1016/j.ejim.2021.04.020. Epub 2021 May 8. PMID: 33972152.