

Review Article

Overview on Mixed Connective-Tissue Disease (MCTD)

Abstract:

Most scholars regard mixed connective tissue disease (MCTD) to be a separate illness, whereas some suggest it might be a precursor to a distinct connective tissue disease, such as SLE, SSc, or overlap syndrome. There are no distinct clinical symptoms of MCTD, and clinical presentations vary greatly across individuals. Since the first description, the categorization as a distinct clinical entity has been debated, particularly because individuals with **U1 snRNP** may eventually match the diagnostic criteria of other 'specified' CTDs. Furthermore, not all investigations have corroborated Sharp's initial definition of MCTD as a benign illness with no organ involvement and a quick response to low-dose glucocorticoids. Mixed connective tissue disease is an uncommon illness with an unknown frequency. Raynaud's phenomenon, arthralgias, swollen joints, esophageal dysfunction, muscular weakness, and sausage-like fingers are the most prevalent clinical signs of mixed connective disease, along with the presence of anti-**ribonucleoprotein (RNP)** antibodies. Although several sets of clinical criteria have been offered, there is no agreement on which is the most accurate. MCTD frequently mimics various illnesses and can be readily misdiagnosed. However, many physicians like the Alarcon-Segovia and Villarreal criteria, owing to their simplicity and wide application, here is little consensus on the initial or long-term therapy of MCTD, particularly the use of low-dose glucocorticoids, antimalarial, and immunosuppressive medications in varied clinical settings. In this article, we we'll be looking at the disease epidemiology, assessment and treatment.

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Keywords: connective tissue, arthralgias, joints, pulmonary artery hypertension

Introduction:

Anti-U1-ribonucleoprotein (RNP), previously known as an antibody to extractable nuclear antigen, is a rare systemic autoimmune disease with overlapping features of at least two connective tissue diseases, including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), and rheumatoid arthritis (RA). Most scholars regard MCTD to be a separate illness, whereas some suggest it might be a precursor to a distinct connective tissue disease, such as SLE, SSc, or overlap syndrome. There are no distinct clinical symptoms of MCTD, and clinical presentations vary greatly across individuals. [1-3]. The incidence and prevalence of MCTD were estimated to be 2.1 per million per year and 3.8 per 100,000 persons, respectively, in research done in Norway. The female to male ratio was 3.3, with a mean age of 37.9 years at diagnosis. Sharp and his colleagues first defined MCTD as a minor condition with a favourable prognosis and a satisfactory response to steroids. Sharp's results are validated by Hajas et al., who reported a 5-, 10-, and 15-year survival rate of 98 percent, 96 percent, and 88 percent, respectively. [4-7] One of the often-used diagnostic criteria is Alarcon-Segovia, which includes a high titer of positive anti-U1-RNP (greater than 1 per 1600) and three or more of the preceding clinical features: Raynaud phenomenon, hand edoema, synovitis, histologically verified myositis, and acrosclerosis. [1,8].

Since the first description, the categorization as a distinct clinical entity has been debated, particularly because individuals with U1 snRNP may eventually match the diagnostic criteria of other 'specified' CTDs. Furthermore, not all investigations have corroborated Sharp's initial definition of MCTD as a benign illness with no organ involvement and a quick response to low-dose glucocorticoids. Furthermore, there are no universally accepted categorization standards. Nonetheless, some differences, such as pulmonary disease, indicate to a distinct disease pattern. [9-13].

Although everyone agrees that the "MCTD" discovery process was uncommon and that many questions remain unresolved, some in the rheumatology world still consider it a separate illness. [14-18] This is because certain anti-RNP-positive individuals appear to have a similar clinical picture with overlapping ARD characteristics, a proclivity for the gradual development of PAH (pulmonary

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arterial hypertension ([PAH](#)) and ~~ILD~~ (interstitial lung disease ([ILD](#))), and very infrequent renal or neurological involvement. Some have interpreted the discovery of a genetic connection between HLA haplotype and anti-U1RNP antibodies as supporting the idea of MCTD. Other research, however, found that this relationship did not correspond with clinical illness manifestation, but rather with antibody production. [14, 19-23]

What exactly is illness remission? There is no established disease activity measure or indicator for MCTD. The clinical characteristics of MCTD coincide with those of SSc, SLE, idiopathic inflammatory myopathy (IIM), and RA. SLEDAI-2 K is a validated activity metric for SLE patients. A large SSc cohort was recently used to develop and validate the preliminary European Scleroderma Trials and Research Group (EUSTAR) disease activity score. MCTD activity can be suitably assessed by combining the SLEDAI-2 K and EUSTAR activity indexes. The SLEDAI-2 K was deemed adequate for measuring myositis and arthritis activity in MCTD patients by some researchers. Remission off therapy necessitated the patient receiving no immune-modulating therapy other than maintenance HCQ. [24]

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Epidemiology:

Mixed connective tissue disease is an uncommon illness with an unknown frequency. The incidence of MCTD was 1.9 per 100,000 individuals per year in population-based research conducted in Olmsted County, Minnesota. The average age of diagnosis was 48 years, and 84% of those afflicted were female. [25] The incidence of MCTD in the Norwegian population was 2.1 per million per year, the female to male ratio was 3.3 to 1, and the mean age at diagnosis was 37.9 years, according to research. This illness affects all races and has comparable clinical signs in all ethnic groups. [1,26]

According to global data, deforming arthritis may be found in roughly 60% of MCTD patients. In one research, around 70% of individuals tested positive for rheumatoid factor. Although the total frequency of arthritis was virtually the same (69.4 percent) in another research, just 6 people had deforming arthritis (5.4 percent). When compared to previous cohorts, a lower number of patients (22.5 percent) showed a positive rheumatoid factor. At this moment, it is unknown if this

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is causality or association, and future study into the pathophysiology of the illness may shed light on this. [4,27,28]

Assessment:

Raynaud's phenomenon, arthralgias, swollen joints, esophageal dysfunction, muscular weakness, and sausage-like fingers are the most prevalent clinical signs of mixed connective disease, along with the presence of anti-ribonucleoprotein (RNP) antibodies. However, organ involvement is more widespread than initially described. The condition can be fatal, causing symptoms in the lungs, kidneys, cardiovascular system, gastrointestinal tract, and central nervous system. The presence of pulmonary illness is connected with the poorest prognosis and high mortality. Although several clinical criteria have been presented, there is no agreement on which is the most accurate. There is no complete consensus on therapy, and the first perception of a successful response to modest doses of steroids is not necessarily the case. [29]

A very high titer ANA and anti U1-RNP antibodies are the initial clues to a diagnosis of MCTD. It is also vital to note the absence of other particular autoantibodies. Antibodies to double-stranded DNA (dsDNA), Sm, and SSA/SSB are often observed as a temporary condition, but when they are the dominant antibody, the clinical history is more consistent with SLE. [30]

CPGs for diagnosing MCTD (diagnostic criteria): Although several sets of clinical criteria have been offered, there is no agreement on which is the most accurate. MCTD frequently mimics various illnesses and can be readily misdiagnosed as systemic sclerosis, rheumatoid arthritis, or so-called overlap syndromes. It is impossible to get a consensus on the presence of MCTDs and illness CPGs without a standardised and accepted set of criteria. Furthermore, such categorization criteria would make it easier to construct registries to gather a sufficient number of patients with MCTD in order to study the course and prognosis. The classification criteria would also allow for the evaluation of biomarkers, specifically the potential diagnostic/prognostic role of antibodies targeting U1 snRNP and/or in combination with the detection of autoantibodies that could previously characterise more defined CTDs such as anti-SCL70, anti-

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CCP, anti-Jo1, anti-Sm, anti-ds-DNA-associated entities for defining early progression. [9]

Although there are no American College of Rheumatology guidelines for MCTD categorization, numerous classification criteria have been published. Many physicians like the Alarcon-Segovia and Villarreal criteria, owing to their simplicity and wide application. They are depicted below. These criteria include some of the early characteristics of MCTD. [30]

Serologic: anti-RNP with a titer of $\geq 1:1,600$

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Clinical Features:

- Myositis or synovitis plus two of the following
- Raynaud's phenomenon
- sclerodactyly/acrosclerosis
- edoema of the hands
- synovitis
- myositis

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Chest X-ray: A chest X-ray can be used to diagnose pulmonary infiltrates, pleural effusion, and cardiomegaly. Patients with pulmonary hypertension may experience pulmonary artery dilatation. While X-ray in joints may reveal tiny, asymmetrical periarticular erosions. Soft tissue edoema, deformities, and destructive arthritis similar to psoriatic arthritis can occur. Periarticular osteopenia and aseptic necrosis are uncommon. [1]

Echocardiogram can reveal pericardial effusion, mitral valve prolapses, left ventricular hypertrophy, and pulmonary hypertension-related abnormalities.

EKG abnormalities include hemiblock, bundle branch block, atrioventricular block, pericarditis-related alterations, and pericardial effusion.

Testing for pulmonary function: interstitial lung disease causes a decrease in carbon monoxide diffusion capacity, forced vital capacity, forced expiratory volume, and six-minute walk tests. [1]

CPGs on MCTD initial and follow-up assessments: On the one hand, MCTD is characterised as a possibly moderate and frequently curable illness by some. On the other side, the condition is incurable and can be harmful or even fatal,

including involvement of the lungs, kidneys, gastrointestinal tract, and central nervous system. In this case, early and targeted action will undoubtedly result in a better outcome. The presence of pulmonary illness is connected with the poorest prognosis and high mortality. It would undoubtedly be beneficial to create and verify a (composite) disease activity score for MCTD that takes into consideration all relevant signs and symptoms in order to enhance care. Clinicians would benefit from agreement on the frequency of follow-up evaluations during the course of illness based on guidelines. [9]

Management:

The therapy of "MCTD" is not widely addressed. According to Hajas et al., 219 of 280 patients (78.2%) received high-dose steroid (more than 1 mg/kg/day methylprednisolone), 209 (74.6%) received cytotoxic agent (methotrexate, cyclophosphamide, azathioprine), and 42 (15%) received anti-TNF. Cappelli et al. observed that 58 percent of patients were given immunosuppressants (cyclophosphamide, cyclosporine, mofetil mycophenolate, azathioprine, methotrexate, leflunomide), 82 percent were given glucocorticoids (no dosage was given), and 45 percent were given antimalarial medications. As a result, in these investigations, the majority of patients required immunosuppressive therapy. In accordance with current well-defined ARD guidelines, treatment varied with organ evolution. [14]

Symptomatic care of Raynaud's phenomenon involves avoiding coffee, smoking, cold temperatures, and trauma. Oral calcium channel blockers (CCB), such as nifedipine, can reduce peripheral resistance. Prostaglandins given intravenously and nitroglycerin applied topically are both beneficial. There have been cases of Raynaud's phenomenon responding to rituximab. NSAIDs and hydroxychloroquine are commonly used to treat arthritis and arthralgia. Corticosteroids and methotrexate can be used to treat refractory synovitis. [1]

There is little consensus on the initial or long-term therapy of MCTD, particularly the use of low-dose glucocorticoids, antimalarial, and immunosuppressive medications in varied clinical settings. Patients with MCTD are often treated based on commonalities with other CTDs or through organ-based care. Classification

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criteria would therefore allow for clinical studies on treatment therapies. Furthermore, comorbidities (such as osteoporosis, atherosclerosis, and so on) and unique situations (such as pregnancy, family planning, and so on) should be addressed. Overall, the ERN-ReCONNET MCTD group agrees on the importance of evidence-based clinical practise guidelines for MCTD therapy. Such guidelines, without a doubt, necessitate meticulous data gathering from a larger number of patients, as well as coordination among specialists and registers from other nations. [9].

Steroids are frequently less effective in treating pulmonary hypertension. CCB is administered to patients who react to a vasodilator challenge during right cardiac catheterization. The effectiveness of warfarin anticoagulation is uncertain. Therapeutic options include prostaglandins (epoprostenol), endothelin receptor antagonists (ambrisentan), phosphodiesterase 5 inhibitors (sildenafil), and immunosuppression with corticosteroids and cyclophosphamide. Steroids can also help with esophageal issues. Proton pump inhibitors (PPI), lifestyle, and dietary changes, such as raising the head of the bed and avoiding food triggers, are used to treat gastroesophageal reflux disease (GERD). If twice-daily PPI medication fails, prokinetics and stomach fundoplication may be considered. Prokinetics are required for esophageal motility dysfunction. Patients with malabsorption should avoid lactose, and medium-chain triglycerides should replace long-chain fatty acids. [1]

Discussion:

MCTD was initially characterised in 1972 as a disease condition with overlapping symptoms of systemic sclerosis, systemic lupus erythematosus (SLE), and polymyositis linked with antibodies to RNase sensitive extractable nuclear antigen. MCTD became the first rheumatic illness condition to be described by a serologic test when the antigen was identified as polypeptides on the U1 ribonuclear protein component of the splicesome (U1RNP). Over the last 30 years, there has been ongoing dispute about whether MCTD is a "distinct clinical entity." With long-term follow-up research, the early misperception that it had a reasonably excellent prognosis has not survived the test of time. These have revealed a tendency for MCTD to progress to SLE or systemic sclerosis, as well as

pulmonary hypertension and scleroderma renal crises as major causes of mortality. MCTD is a relevant concept in clinical practise as long as we recognise that our understanding of the clinical aspects linked with anti-U1RNP has developed over time. The evidence of shared etiopathological processes underlying the formation of antibodies to U1 RNP and their associated clinical characteristics will determine if it may be credited with the title "disease." [31]

Cappelli et al. found 161 patients in 15 tertiary Italian hospitals. Patients included had "MCTD" diagnosed according to expert opinion and were categorised based on chart review using the three main sets of criteria (Kasukawa, Alarcón-Segovia, and Sharp). Following a chart review, sixteen patients (9.9%) did not meet any diagnostic criteria. Notably, individuals who met the criteria for "MCTD" and another ARD at the conclusion of the research were regarded to have "MCTD." As a result, overlap and progression to other ARDs were only judged to have happened in individuals who no longer met any "MCTD" criteria. Anti-RNP data were not available for 22 patients (14%). [14,32]

PAH (pulmonary artery hypertension (**PAH**)) is a major cause of death in MCTD and is likely underdiagnosed. Different studies have calculated the prevalence of PAH in MCTD in different ways. Norwegian multicenter research suggested a frequency of 3.4 percent, whereas others reported a prevalence ranging from 14 to 18 percent. [33-34] Male gender, a higher anti-U-1 RNP titer, and the lack of arthritis were found as predictors of ILD in the Norwegian research. In Benjamin Chaigne's research no such link was discovered. When compared to western statistics, renal involvement was less prevalent (17 percent versus 40%). The vast majority of individuals developed membranous glomerulonephritis. In that study also, esophageal dysfunction was also less common (28.8 %). When compared to the other literature, these characteristics indicate fundamental variations in the MCTD phenotype in Indian individuals. [4, 35-36]

Conclusion:

There are no distinct clinical symptoms of MCTD, and clinical presentations vary greatly across individuals. Although several sets of clinical criteria have been offered, there is no agreement on which is the most accurate. MCTD frequently

mimics various illnesses and can be readily misdiagnosed. However, many physicians use the Alarcon-Segovia and Villarreal criteria, owing to their simplicity and wide application. There is little consensus on the initial or long-term therapy of MCTD. Many trials are needed to develop well established guidelines for the treatment regimens.

References:

1. Sapkota B, Al Khalili Y. Mixed Connective Tissue Disease. [Updated 2022 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK542198/>.
2. 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):148-59.
3. Bennett RM, O'Connell DJ. Mixed connective tissue disease: a clinicopathologic study of 20 cases. *Semin Arthritis Rheum.* 1980 Aug;10(1):25-51.
4. John KJ, Sadiq M, George T, et al. Clinical and Immunological Profile of Mixed Connective Tissue Disease and a Comparison of Four Diagnostic Criteria. *Int J Rheumatol.* 2020;2020:9692030. Published 2020 Jan 29. doi:10.1155/2020/9692030.
5. Sharp G. C., Irvin W. S., Tan E. M., Gould R. G., Holman H. R. Mixed connective tissue disease-an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA) *The American Journal of Medicine.* 1972;52(2):148-159. doi: 10.1016/0002-9343(72)90064-2.
6. Gunnarsson R., Molberg Ø., Gilboe I.-M., Gran J. T., PAHNOR1 Study Group The prevalence and incidence of mixed connective tissue disease: a national multicentre survey of Norwegian patients. *Ann Rheum Dis.* 2011;70(6):1047-1051. doi: 10.1136/ard.2010.143792.

7. Hajas A., Szodoray P., Nakken B., et al. Clinical course, prognosis, and causes of death in mixed connective tissue disease. *The Journal of Rheumatology*. 2013;40(7):1134–1142. doi: 10.3899/jrheum.121272.
8. Alarcón-Segovia D, Cardiel MH. Comparison between 3 diagnostic criteria for mixed connective tissue disease. Study of 593 patients. *J Rheumatol*. 1989 Mar;16(3):328-34.
9. Chaigne B, Scirè CA, Talarico R, et al. Mixed connective tissue disease: state of the art on clinical practice guidelines. *RMD Open*. 2018;4(Suppl 1):e000783. Published 2018 Oct 18. doi:10.1136/rmdopen-2018-000783.
10. Institute of Medicine (US) Committee to Advise the Public Health Service on Clinical Practice Guidelines In: Field MJ, Lohr KN, Clinical practice guidelines: directions for a new program. Washington (DC): National Academies Press (US), 1990.
11. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines In: Graham R, Mancher M, Miller Wolman D, Clinical practice guidelines we can trust. Washington (DC): National Academies Press (US), 2011.
12. Brouwers MC, Kho ME, Browman GP, et al.. AGREE II: advancing guideline development, reporting and evaluation in health care. *Can Med Assoc J* 2010;182:E839–42. 10.1503/cmaj.090449.
13. Brouwers MC, Kho ME, Browman GP, et al.. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. *Can Med Assoc J* 2010;182:1045–52. 10.1503/cmaj.091714.
14. Alves MR, Isenberg DA. "Mixed connective tissue disease": a condition in search of an identity. *Clin Exp Med*. 2020;20(2):159-166. doi:10.1007/s10238-020-00606-7.
15. Aringer M, Steiner G, Smolen JS. Does mixed connective tissue disease exist? Yes. *Rheum Dis Clin N Am*. 2005;31(3):411–420.
16. Martínez-Barrio J, Valor L, López-Longo FJ. Facts and controversies in mixed connective tissue disease. *Med Clin (Barc)* 2018;150(1):26–32.
17. Farhey Y. Mixed connective tissue disease (MCTD)—a coming of age. *Curr Rheumatol Rev*. 2012;8(1):20–29.

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18. Aringer M, Smolen JS. Mixed connective tissue disease: what is behind the curtain? *Best Pract Res Clin Rheumatol.* 2007;21(6):1037–1049.
19. Black CM, Maddison PJ, Welsh KI, Bernstein R, Woodrow JC, Pereira RS. HLA and immunoglobulin allotypes in mixed connective tissue disease. *Arthritis Rheumatol.* 1988;31(1):131–134.
20. Hoffman RW, Rettenmaier LJ, Takeda Y, et al. Human autoantibodies against the 70-kd polypeptide of u1 small nuclear rnp are associated with HLA-DR4 among connective tissue disease patients. *Arthritis Rheumatol.* 1990;33(5):666–673.
21. Ruuska P, Hämeenkorpri R, Forsberg S, et al. Differences in HLA antigens between patients with mixed connective tissue disease and systemic lupus erythematosus. *Ann Rheum Dis.* 1992;51(1):52–55.
22. Genth E, Zarnowski H, Mierau R, Wohltmann D, Hartl PW. HLA-DR4 and Gm(1,3;5,21) are associated with U1-nRNP antibody positive connective tissue disease. *Ann Rheum Dis.* 1987;46(3):189–196.
23. Gendi NS, Welsh KI, Van Venrooij WJ, Vancheeswaran R, Gilroy J, Black CM. HLA type as a predictor of mixed connective tissue disease differentiation. Ten-year clinical and immunogenetic followup of 46 patients. *Arthritis Rheum.* 1995;38(2):259–266.
24. Reiseter S, Gunnarsson R, Corander J, et al. Disease evolution in mixed connective tissue disease: results from a long-term nationwide prospective cohort study. *Arthritis Res Ther.* 2017;19(1):284. Published 2017 Dec 21. doi:10.1186/s13075-017-1494-7
25. Ungrasert P, Crowson CS, Chowdhary VR, Ernste FC, Moder KG, Matteson EL. Epidemiology of Mixed Connective Tissue Disease, 1985-2014: A Population-Based Study. *Arthritis Care Res (Hoboken).* 2016 Dec;68(12):1843-1848.
26. Gunnarsson R, Molberg O, Gilboe IM, Gran JT., PAHNOR1 Study Group. The prevalence and incidence of mixed connective tissue disease: a national multicentre survey of Norwegian patients. *Ann Rheum Dis.* 2011 Jun;70(6):1047-51.

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27. Mimura Y., Ihn H., Jinnin M., Asano Y., Yamane K., Tamaki K. Rheumatoid factor isotypes in mixed connective tissue disease. *Clinical Rheumatology*. 2006;25(4):572–574. doi: 10.1007/s10067-005-0185-y.
28. Venables P. J. Mixed connective tissue disease. *Lupus*. 2006;15(3):132–137. doi: 10.1191/0961203306lu2283rr.
29. 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. doi: 10.1016/j.berh.2012.01.009. PMID: 22424193.
30. Pepmueller PH. Undifferentiated Connective Tissue Disease, Mixed Connective Tissue Disease, and Overlap Syndromes in Rheumatology. *Mo Med*. 2016;113(2):136-140.
31. Venables PJ. Mixed connective tissue disease. *Lupus*. 2006;15(3):132-7. doi: 10.1191/0961203306lu2283rr. PMID: 16634365.
32. Cappelli S, Bellando Randone S, Martinović D, et al. ‘To be or not to be’, ten years after: evidence for mixed connective tissue disease as a distinct entity. *Semin Arthritis Rheum*. 2012;41(4):589–598.
33. Gunnarsson R., Andreassen A. K., Molberg Ø., et al. Prevalence of pulmonary hypertension in an unselected, mixed connective tissue disease cohort: results of a nationwide, Norwegian cross-sectional multicentre study and review of current literature. *Rheumatology*. 2013;52(7):1208–1213. doi: 10.1093/rheumatology/kes430.
34. Vegh J., Szodoray P., Kappelmayer J., et al. Clinical and immunoserological characteristics of mixed connective tissue disease associated with pulmonary arterial hypertension. *Scandinavian Journal of Immunology*. 2006;64(1):69–76. doi: 10.1111/j.1365-3083.2006.01770.x.
35. Reisetter S., Gunnarsson R., Mogens Aaløkken T., et al. Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. *Rheumatology*. 2018;57(2):255–262. doi: 10.1093/rheumatology/kex077.
36. Fagundes M. N., Caleiro M. T. C., Navarro-Rodriguez T., et al. Esophageal involvement and interstitial lung disease in mixed connective tissue

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disease. Respiratory Medicine. 2009;103(6):854–860. doi:
10.1016/j.rmed.2008.12.018.

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