Castleman-Like Lymphadenopathy in a Patient with Mixed Connective Tissue Disease: A Case Report and Review of the Literature

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SUMMARY
Differentiating reactive lymphadenopathies in the context of autoimmune disease from Idiopathic Multicentric Castleman Disease (iMCD) poses a significant diagnostic challenge. Castleman-like histological features have been described in various autoimmune disorders, necessitating a strict and comprehensive integration of clinical and laboratory findings to reach the correct diagnosis. Although the Castleman Disease Collaborative Network (CDCN) consensus guidelines list several autoimmune conditions as exclusion criteria for an iMCD diagnosis, mixed connective tissue disease (MCTD) is not currently among them. We report the case of a 77-year-old woman presenting with fatigue, Raynaud's phenomenon, sclerodactyly, mild generalized lymphadenopathy, in whom the lymph node biopsy revealed a Castleman-like histology. The absence of systemic inflammatory symptoms and the presence of high-titer anti-U1-RNP antibodies were, however, inconsistent with iMCD, favouring the diagnosis of a reactive Castleman-like lymphadenitis secondary to MCTD. This report highlights that Castleman-like lymphadenopathy can occur in MCTD, closely mimicking iMCD. Therefore, in patients with autoimmune diseases not explicitly listed among the CDCN exclusion criteria, comprehensive clinicopathological integration is essential to avoid misdiagnosis and potentially inappropriate anti-IL-6-based therapy.

Keywords: Mixed connective tissue disease – Castleman-like lymphadenopathy – Autoimmune disease – Sclerodactyly – Raynaud's phenomenon - anti-U1-RNP

Castleman-like lymfadenopatie u pacienta se smíšenou chorobou pojiva: kazuistika a přehled literatury

SOUHRN
Odlišení reaktivních lymfadenopatií v kontextu autoimunitních onemocnění od idiopatické multicentrické Castlemanovy choroby (iMCD) představuje významnou diagnostickou výzvu. Histologické znaky podobné Castlemanově chorobě byly popsány u různých autoimunitních onemocnění, což vyžaduje striktní a komplexní integraci klinických a laboratorních nálezů k dosažení správné diagnózy. Ačkoli konsenzuální doporučení Castleman Disease Collaborative Network (CDCN) uvádějí několik autoimunitních onemocnění jako vylučovací kritéria pro diagnózu iMCD, smíšené onemocnění pojiva (MCTD) mezi nimi v současnosti uvedeno není. Popisujeme případ 77leté ženy s únavou, Raynaudovým fenoménem, sklerodaktylií a mírnou generalizovanou lymfadenopatií, u níž biopsie lymfatické uzliny prokázala histologii podobnou Castlemanově chorobě. Absence systémových zánětlivých příznaků a přítomnost vysokých titrů protilátek anti-U1-RNP však nebyly v souladu s iMCD a spíše podporovaly diagnózu reaktivní Castleman-like lymfadenitidy sekundární k MCTD.
Tato kazuistika zdůrazňuje, že Castleman-like lymfadenopatie se může vyskytovat i u MCTD a může velmi těsně napodobovat iMCD. U pacientů s autoimunitními onemocněními, která nejsou výslovně uvedena mezi vylučovacími kritérii CDCN, je proto nezbytná důkladná klinicko-patologická integrace, aby se předešlo chybné diagnóze a potenciálně nevhodné terapii založené na blokádě IL-6.

Klíčová slova: smíšené onemocnění pojiva – Castleman-like lymfadenopatie – autoimmunitní onemocnění – sklerodaktylie – Raynaudův fenomén - anti-U1-RNP

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Castleman disease (CD) represents a spectrum of disorders characterized by distinctive but not specific lymph node histopathology and clinical manifestations, including systemic inflammation, cytopenias, and, in severe cases, life-threatening multiorgan dysfunction (1-4). Significant advances in the understanding, diagnosis, and management of CD have been achieved by the Castleman Disease Collaborative Network (CDCN) consensus guidelines for diagnostic and therapeutic stratification (2, 5-7). According to these criteria, CD is subdivided into unicentric CD (UCD) and multicentric CD (MCD), that can be further categorized into three main subtypes (1, 2). Among these the idiopathic form is further divided into iMCD-TAFRO (defined by thrombocytopenia, acites (anasarca), bone-marrow reticulin fibrosis, renal impairment, and organomegaly), Idiopathic Plasmacytic Lymphadenopathy (IPL) (characterized by thrombocytosis, hypergammaglobulinemia, and a less severe clinical presentation), and iMCD not otherwise specified (8, 9). The etiology of iMCD remains incompletely understood, although excessive production of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) are recognized as key pathogenic mediators (1). Patients with iMCD usually present with multiple enlarged lymph nodes and a vari-

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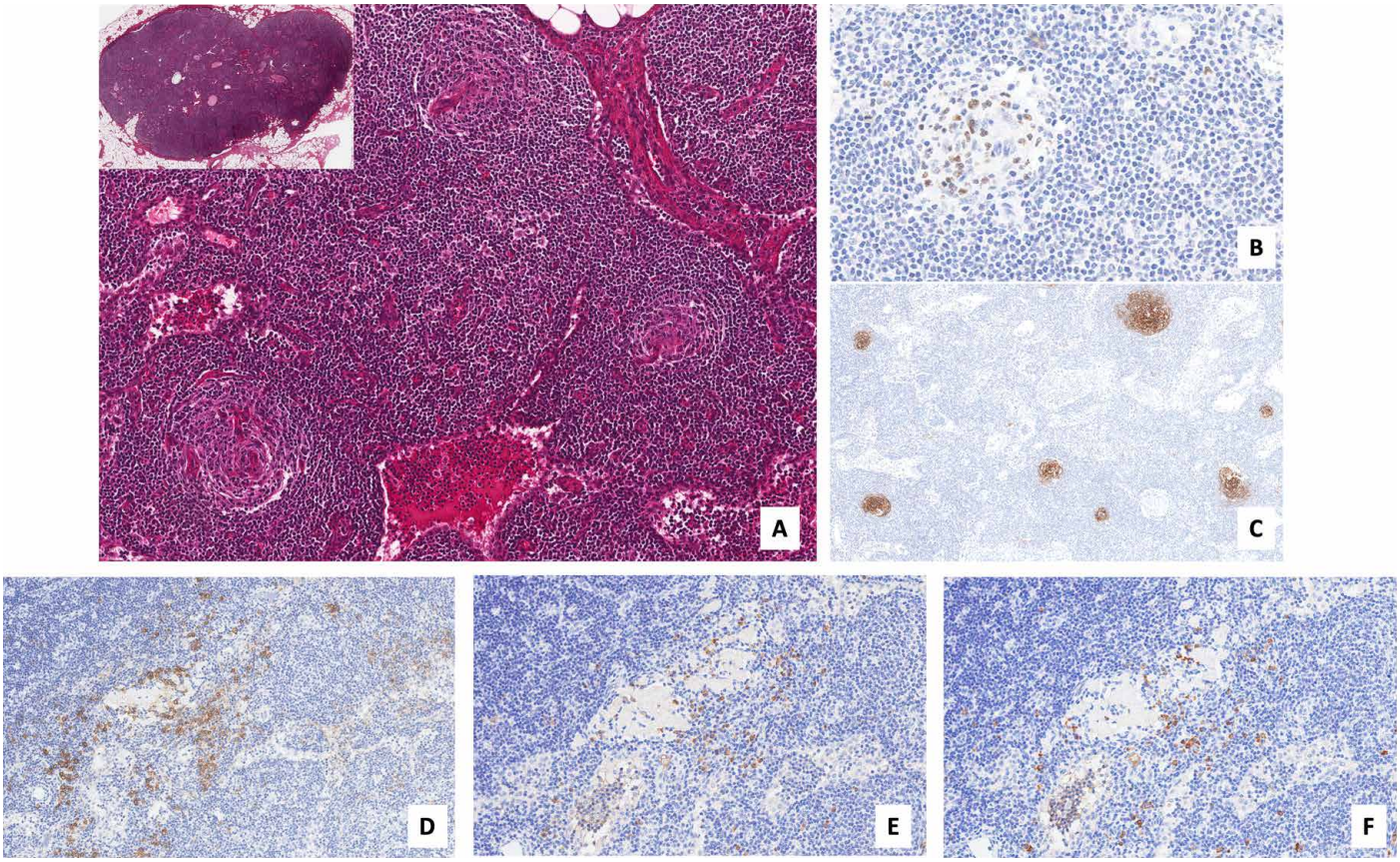

Fig. 1. Histological features of the excised lymph node. Supraclavicular lymph node with largely preserved architecture (A, upper insert, hematoxylin and eosin (H&E), original magnification (o.m.) x15). The lymphoid follicles showed germinal centers (GCs) with differing degrees of regression, some of which were penetrated by radially oriented hyalinized capillaries and surrounded by concentrically arranged mantle-zone lymphocytes (A, H&E, o.m. x100). The regressed GCs contained a fewer number of GC cells (B: BCL6, o.m. x200) and were centered by a compact meshwork of follicular dendritic cells (C: CD23, o.m. x70). The interfollicular areas were expanded and contained numerous small blood vessels, and a mild polytypic plasma cell infiltrate (D: CD138, E: kappa, F: lambda, o.m. x200).

able constellation of systemic manifestations —fever, fatigue, weight loss, night sweats, serous effusions, and skin lesions (i.e. cherry angiomas)— accompanied by laboratory abnormalities such as anemia, thrombocytopenia or thrombocytosis, elevated ESR (Erythrocyte Sedimentation Rate) and CRP (C-Reactive Protein), polyclonal hypergammaglobulinemia, hypoalbuminemia, and renal dysfunction. The clinical course is often relapsing and remitting, requiring systemic therapy with anti-IL-6 agents (e.g., siltuximab) or anti-CD20 drugs (e.g. rituximab) (7, 10). From a histopathological standpoint, CD is classified into hyaline-vascular (in UCD) or hypervascular (in MCD) type (HV-CD), plasma-cell type (P-CD), and mixed (mixed-CD) type, depending on the degree of follicular regression or hyperplasia and the extent of interfollicular vascular proliferation and plasmacytosis (2). Because CD-like histopathological and clinical features may also appear in other diseases, rigorous exclusion of alternative causes is essential before establishing an iMCD diagnosis (11-14). Among these mimicking conditions, the CDCN guidelines listed infections, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), adult-onset Still's disease, juvenile idiopathic arthritis, autoimmune lymphoproliferative syndrome (ALPS), HIV-associated lymphadenopathy, and both Hodgkin and non-Hodgkin lymphomas. Other autoimmune diseases that may present with CD-like lymphadenopathy, such as mixed connective tissue disease (MCTD), are less well characterized and do not necessarily exclude a diagnosis of CD (13). MCTD is a rare systemic autoimmune disease characterized by the presence of anti-U1-ribonucleoprotein (RNP) antibodies, Raynaud phenomenon and signs/symptoms of at least 2 overlapping connective tissue diseases, including SLE, systemic sclerosis, polymyositis (15, 16). Given the anti-U1-RNP antibody is the hallmark of MCTD, it is believed that it plays a role in the pathogenesis of MCTD with two main proposed mechanisms. The first involves the direct binding to endothelial cells through U1 RNP peptides or recognition of nucleosome RNP fragments in endothelial cell apoptotic blebs (17, 18). This may lead to the vascular diseases (Raynaud phenomenon), skin sclerosis, and pulmonary hypertension. The second is through immune complex formation, which can activate the complement cascade and lead to tissue inflammation and damage, such as myositis, arthritis, and interstitial lung disease (17, 18). The inflammatory cascade induced by the anti-U1 RNP antibodies is also responsible for the elevated serum levels of IL-6, IL-1, TNF-alpha, and IFN-gamma observed in patients with MCTD (17, 19, 20). Herein we present the case of a patient with MCTD with CD-like lymphadenopathy, for which in accordance with CDCN recommendations, we employed a comprehensive, multidisciplinary evaluation integrating clinical, serological, radiologic, and pathological findings to assess the correct diagnosis (1, 5).

CASE REPORT

A 77-year-old female was referred to our hospital for evaluation of unexplained fatigue and mild generalized lymphadenopathy. She denied fever, weight loss, or night sweats. Clinical examination revealed non-tender lymph nodes in the supraclavicular region. Initial laboratory studies showed

normal hematologic, hepatic, and renal parameters. Inflammatory markers (ESR, CRP) were within normal limits. Ultrasound and CT scans revealed multiple small lymph nodes (<1.5 cm) in both supradiaphragmatic and infradiaphragmatic stations, along with mild splenomegaly (maximal craniocaudal dimension of 13 cm). An excisional biopsy of a supraclavicular lymph node was performed. Histologically, the lymph node architecture was largely preserved, featuring patent sinuses and normal compartmentalization of the B- and T-cell areas (Figure 1). The B-cell zones displayed irregularly shaped lymphoid follicles whose germinal centres (GCs) showed variable degrees of regression (grade 2 according to the CDCN classification), containing a lower number of GC cells (CD10+/-, BCL6+/-, BCL2-) and with moderate prominence of CD21+, CD23+ follicular dendritic cells (FDCs) (grade 2 according to the CDCN classification). Characteristically, some germinal centres were penetrated by radially oriented hyalinized capillaries, creating a "lollipop" appearance. These were surrounded by mantle-zone lymphocytes, occasionally concentrically arranged forming an "onion skin" pattern. The interfollicular areas contained a moderate proliferation of small blood vessels (grade 2 according to the CDCN classification), abundant reactive T cells, scattered immunoblasts, and a few polytypic plasma cells (grade 0 according to the CDCN classification) (Figure 1). Immunostaining for human herpes virus 8 (LANA-1) and in situ hybridization for EBER were both negative. The overall lymph node findings were interpreted as a reactive Castleman-like lymphadenitis, necessitating integration with clinical, radiological and laboratory data to differentiate HV-CD from an autoimmune or infectious etiology. Additional clinical investigations revealed sclerodactyly and a history of episodic Raynaud's phenomenon. The patient did not report other systemic signs. Serologic tests demonstrated the presence of anti-nuclear (ANA) antibodies and high titers of anti-U1 RNP antibodies. Although the excised lymph node exhibited some morphological features reminiscent of Castleman disease—including regressed germinal centers, concentric mantle zones, and mildly increased vascular proliferation—the overall findings did not meet the established diagnostic criteria for iMCD. Specifically, the absence of systemic inflammatory symptoms and serological inflammatory markers, coupled with the presence of high-titer anti-U1 RNP antibodies and signs of connective tissue diseases, was more consistent with an underlying autoimmune process. Therefore, integrating the histopathological, serological, and clinical data, the lymphadenopathy was interpreted as a reactive Castleman-like lymphadenitis secondary to MCTD rather than an iMCD associated with MCTD.

DISCUSSION

The presence of regressed germinal centers, concentric mantle zones, marked vascular proliferation, and prominent interfollicular plasmacytosis can closely resemble the spectrum of histological lesions seen in iMCD. However, Castleman-like morphology alone does not establish a diagnosis of Castleman Disease (CD), as these findings may also occur in reactive conditions secondary to immune dysregulation or infection (11-14). According to the CDCN guidelines, a diagnosis of iMCD necessitates both characteristic histopathology and compatible systemic clinical and laboratory findings, as well as the exclusion of alternative conditions, including selected autoimmune and autoinflammatory diseases when the disease-specific clinical criteria are met (11, 13, 14). These criteria, however, do not specifically address less common overlap syndromes, such as MCTD. Indeed, CD-like histopathological changes have been described in a variety of established autoimmune diseases, such as SLE, RA, and ALPS (11-14), but are also reported—though less frequently—in MCTD (21-26). Several reports, summarized in Table 1, highlight cases of concomitant diagnosis of MCTD and CD (21-26). On the contrary, in our case we were unable to diagnose a MCD due to unmet diagnostic criteria. However, given that MCTD is also a multisystem autoimmune disorder with immune-mediated lymphoid activation, it remains uncertain whether its presence should be regarded as an exclusion criterion for iMCD or whether both conditions may genuinely coexist. This ambiguity has important implications for the interpretation of Castleman-like lymphadenopathy in patients with connective tissue diseases other than SLE or RA.

In MCTD the autoimmune background might provide a plausible mechanism for CD-like histological changes. Immune activation of the downstream inflammatory cascade driven by anti-U1-RNP antibodies induces elevated serum levels of IL-6, IL-1alpha, TNF-alpha, and IFN-gamma, (17, 19, 20) which are responsible of the broad histologic heterogeneity observed in MCTD-associated lymphadenopathy. In Table 1 and 2, we summarize reported cases of MCTD with available lymph node histology. The lesions span a wide morphologic spectrum, including sarcoid-like granulomatous reactions (27), Kikuchi-like necrotizing lymphadenitis (28-33), non-specific reactive lymphadenitis (16, 34-39) and lymphadenitis with CD-like changes (21-26).

The distinction between iMCD and autoimmune-driven reactive conditions is clinically critical: misclassification as iMCD could lead to unnecessary anti-IL-6–based therapies, while correct recognition of an autoimmune-driven reactive process allows for appropriate immunomodulatory management. Recognition that Castleman-like morphology may represent a reactive pattern rather than a diagnostic entity prevents the overdiagnosis of iMCD and reinforces the need to interpret lymph node histopathology within the broader clinical and immunological context. In our case, the integration of clinical, serological, and pathological data strongly favoured the diagnosis of reactive Castleman-like lymphadenitis associated with MCTD, thus emphasizing the importance of a multidisciplinary, clinicopathological correlation when evaluating lymphadenopathy with Castleman-like features.

In conclusion, with the present case we highlighted that Castleman disease-like lymphadenopathies may occur as a histological pattern in the context of less characterized autoimmune diseases such as MCTD. A careful multidisciplinary assessment integrating clinical, serological, and pathological findings is therefore essential to distinguish reactive Castleman-like lymphadenitis from iMCD to avoid misdiagnosis and inappropriate treatment.

Tab. 1. Reported cases of CD associated with MCTD.

Authors (year of publication) (Ref)	Age	Sex	Clinical findings	Laboratory findings	Biopsy site	Histology	Final diagnosis	Treatment and FUP
T Nanki (1994) (21)	60	F	Fatigue, cough, pyrexia, splenomegaly, Raynaud's phenomenon, sclerodactyly, pigmentation of the hands, interstitial pneumonitis, arthritis of the wrists, metacarpophalangeal and proximal interphalangeal joints, proximal muscle weakness and atrophy. Multiple enlarged lymph nodes in the neck, axilla, and groin. Left peroneal nerve palsy and sensory disturbance in the left foot, and impaired glucose tolerance	Increase in IgG without any M component, elevated ESR CRP, anemia, ANA+, ENA+ and anti-RNP+. Marked increase of serum IL6 level. Karyotype from peripheral blood cells and lymph node 47, XXX	Cervical and inguinal lymph nodes	PC-CD	MCDassociated with MCTD	Corticosteroid Symptoms improvement And lymph nodes Alive
Chrispal A. (2010) (22)	16	F	Polyarthritis of the small and large joints, Raynaud's phenomenon, malar rash, oral ulcers, photosensitivity and alopecia. Pedal oedema and a rash involving the dorsum of the fingers and toes with intermittent fever. She also complained of a mild non-productive cough. Anasarca and free fluid in the abdomen. Mesangio-proliferative glomerulonephritis. Left hilum mass	Anemia with direct Coombs test (DCT 1+). ANA+, RF+, anti-RNP+, dsDNA-. Complements were low (<60%). Nephrotic range proteinuria and hypo-albuminemia	NB of the left lung hilar mass (8x7 cm)	HV-CD	UCD associated with MCTD	Corticosteroid, Azathioprine Hydroxychloroquine CR of symptoms and reduction of the lung hilar mass Alive
Ashwin Karuppan. V (2024) (23)	56	F	Previous history of hypothyroidism and type 2 diabetes mellitus. Generalized tiredness, abdominal pain, fever, burning micturition, vomiting, black colored stools and bilateral axilla pain. Multiple enlarged hypermetabolic bilateral axillaries and subpectoral lymph nodes	Anemia, significant growth of Enterococcus faecium in urine culture. anti-RNP+	Axillary lymph node	Mixed-CD	MCD associated with MCTD and urinary infection	Steroids and antibiotic Symptoms improvement Alive
Saparov D. (2024) (26)	68	F	Medical history of diabetes mellitus, hypertension, atrial fibrillation, ILD, lymphadenopathy, splenomegaly, malaise, fever, night sweats, and arthralgia of the small joints of the bilateral upper extremities. Diffuse intra-abdominal and axillary adenopathy. Diagnosis of MCTD 6 months earlier.	HIV negative	Axillary lymph node	PC-CD	MCD associated with MCTD	Rituximab Corticosteroids Treated 6 years later with anti-IL6 therapy discontinued due to side effects Symptoms improvement Stable disease Alive
Popović Dragonjić L. (2020) (24)	39	M	Fever, weight loss, incoherent speech, headache with nausea, vomiting, intense neck pain, eyelid drooping and weakness of arms and legs with consequent movement difficulty. The patient was sleepy and confused. Raynaud's syndrome owing to periodic feeling of numbness in hand fingers. Somnolence, disorientation, slurred speech, neck stiffness, positive Brudzinski's neck sign, right eyelid ptosis, bilaterally slightly reduced breath sound, left pretibial edema, bilateral inguinal lymphadenopathy, cachexia, maculopapular rash on trunk and proximal lower extremities. He also has a distal symmetric sensorimotor polyneuropathy, lung fibrosis, bilateral pleural effusion, pericardial effusion and mediastinal and bilateral inguinal lymph nodes, with hepatosplenomegaly. The patient had enhanced accumulation of radiopharmaceutical in the mandibular ramus, right sternoclavicular joint, fifth lumbar vertebra, both femoral necks, left iliac bone, left ischial bone and right knee joint	Increased white blood cells and platelet count, anemia, decreased albumins, increased CRP and procalcitonin level. Anti-RNP+, ANA+. No monoclonal band, but a polyclonal increase in gamma-globulins. Interleukine-6 (IL-6) value of 12.23 pg/mL.	Inguinal lymph node	CD	MCD associated with the osteosclerotic variant of POEMS and MCTD	Prednisone Symptoms improvement Alive
Wojtyś M. (2019) (25)	63	F	Generalized lymphadenopathy, chronic heart and kidney failure, MCTD	NA	Lymph node unknown site	PC-CD	MCD associated with MCTD	Thalidomide Cyclophosphamide Prednisone Dead of multiorgan failure

Abbreviations: ANA, antinuclear antibodies; ENA, extractable nuclear antigen antibodies; anti-RNP, anti–ribonucleoprotein antibodies; anti-dsDNA, anti–double-stranded DNA antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; IgG, immunoglobulin G; IL-6, interleukin 6; ILD, interstitial lung disease; DCT, direct Coombs test; RF, rheumatoid factor; NB, needle biopsy; HIV, human immunodeficiency virus; EBER, Epstein–Barr virus–encoded RNA (in situ hybridization); HHV-8, human herpesvirus 8; TCR, T-cell receptor; IgH, immunoglobulin heavy-chain; IgK, immunoglobulin kappa light-chain; PC-CD, plasma cell–type Castleman disease; HV-CD, hyaline vascular–type Castleman disease; Mixed-CD, mixed-type Castleman disease; MCTD, mixed connective tissue disease; UCD, unicentric Castleman disease; MCD, multicentric Castleman disease; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes; NA, not available; FUP, follow-up.

Tab. 2. Other lymph node histopathological patterns reported in association with MCTD.

Authors (year of publication)	Age	Sex	Clinical findings	Laboratory findings	Biopsy site	Histology/cytology	Final diagnosis	FUP
Fernandes B.M. (2021)	24	F	Diagnosis of KFD on right axillary lymph node after a self-limiting clinical presentation of fever, myalgias, and cervical and axillary lymphadenopathies. Four years later symmetrical polyarthralgia, inflammatory rhythm in the wrists, proximal metacarpophalangeal and interphalangeal joints of the hands, and Raynaud phenomenon. Seven years later, she presented with a painful left axillary adenopathy and fever	Leukopenia, neutropenia, ANA+, anti-RNP+. Liver function tests, CRP, and ESR were normal. Other immunological tests were negative. Seven years later leukopenia, neutropenia, thrombocytopenia, elevation of acute phase markers, transaminases and ferritin with normo triglyceridemia and fibrinogenemia	Axillary	Recurrent KFD with crescentic histiocytes, plasmacytoid monocytes, karyorrhectic debris, and necrosis	MCT-D+KFD	Alive
Gourley I. (1995)	37	F	Sore joints (temporo-mandibular, shoulders, elbows, hips, knees, and neck), early morning stiffness, mild Raynaud's phenomenon, evening rigors, synovitis of both knees and of both elbows and proximal muscle weakness of the shoulder girdle and the thighs. Fine macular, itchy rash over her trunk and arms, irregular spikes of temperature and painful vasculitic lesions of the fingertip pulps. Lymphadenopathy in the cervical region bilaterally, in both axillae, and in the submandibular area	ESR 28 mm/hr, CRP 117 mg/L. High AST, LDH (1182 IU/L) and CPK (824IU/L). ANA+, anti-RNP+, anti-dsDNA negative	Cervical	The normal architecture was partially effaced and replaced by small irregular foci of eosinophilic necrosis with nuclear debris. The necrosis was surrounded by prominent sheets of small histiocytes with clear cytoplasm admixed with scattered small lymphocytes. There was no neutrophil response to the necrosis, and no granulomatous reaction was present. No hematoxylin bodies were identified	MCT-D+KFD	Alive
Pallet N. (2004)	30	F	Painful cervical lymphadenopathy and fever. History of rheumatic fever complicated by mild aortic regurgitation, photosensitivity, Raynaud's phenomenon, eye and mouth dryness, muscle cramps, arthralgia, night sweats, fatigue, tonsillitis, fever, and dysphagia. There was a non-pruriginous macular rash on the legs, and a superficial ulceration was found on the palate	High CPK, LDH, ESR, and CRP. Serum protein electrophoresis showed polyclonal hypergammaglobulinemia. ANA+, anti-RNP+, anti-Sm and anti-dsDNA antibodies were not found	Cervical	Necrotizing non-suppurative histiocytic lymphadenopathy	MCT-D+KFD	Alive
Aqel NM. (1997)	43	F	Fever, generalized weakness, malaise and vomiting. Hashimoto's thyroiditis. Swelling and tightening of the skin of the fingers and face. This was associated with pain and swelling of the joints of all fingers, both wrists and knees. 8kg weight loss in the preceding 2 yr. There was no history of Raynaud's phenomenon, dysphagia, rashes or muscular weakness. Synovitis of the wrists, knees, metacarpophalangeal and proximal interphalangeal joints of the fingers of both hands and sclerodactyly. No telangiectasia or calcinosis. 7 months later bilateral enlargement of axillary lymph nodes	Raised ESR and anemia. RF+, ANA+, anti-RNP+ and anti-Sm+, anti-ds DNA-, anti-SSARo- and SSBLa-. Complement was normal. Polyclonal increase in gamma globulins	Axillary	Expansion of the lymph node cortex and paracortex, localized area of paracortical necrosis rich in apoptotic plasmacytoid monocytes	MCT-D+KFD	NA
Shiokawa (1993)	58	F	Swelling and dysesthesia of both hands and in the left side of her face, and puffiness of the face. She developed high fever and bilateral cervical lymph node enlargement. Esophageal hypomotility. Multiple mononeuritis including the left trigeminal nerve. Sjogren syndrome and hypothyroidism. Raynaud's phenomenon and muscle weakness of both upper arms appeared	Thrombocytopenia, ESR of 10 mm/h, CRP of 3.77 mg/dl, RF+, ANA+, ENA+, anti-RNP+. C3 of 84 mg/dl, C4 of 43 mg/dl, IgG of 2094 mg/dl, IgA of 237 mg/dl, and IgM of 124 mg/dl. Mild liver dysfunction was present. Increase in the gamma globulin fraction	Cervical	Massive necrosis with follicular hyperplasia. Many karyorrhectic nuclear materials and some degenerated neutrophils were observed in the necrotizing foci. Foamy histocytes were present around foci of necrosis. Fibrinoid necrosis of the vessel walls was observed in the necrotic lesions. Hematoxylin bodies were not observed	MCT-D+KFD	NA
Shiokawa S. (1993)	37	F	Dry eyes and dry mouth, polyarthralgia, intermittent high-grade fever, bilateral axillary lymphadenopathy and Raynaud's phenomenon. She also noticed swelling of her face and both hands	Moderately increased ESR (56 mm/h), RF+, ANA+, anti-RNP+. Slightly elevated LDH. Increase in gamma globulin fraction.	Axillary	Massive necrosis with nuclear debris, some histiocytes and dilated capillaries. At the peripheral zone there were numerous plasma cells. Preserved nodal tissue revealed mild reactive follicular hyperplasia. Vascular changes such as fibrinoid necrosis were not observed. Hematoxylin bodies were absent	MCT-D+KFD	NA

Sharma V. (2015)	57	F	Arthritis, Raynaud's phenomenon and rheumatoid nodules/granuloma annulare. Psoriasis. Multiple drug allergies. Pyrexia (38-40°C), flank pain, urinary frequency, erythematous rash on trunk with a diagnosis of pyelonephritis deteriorated into sepsis-like clinical picture. Histology of lymph nodes harvested from the neck bilaterally, peritonsillar area, tracheobronchial region, axillae, groins and small bowel mesentery, as well as the spleen, showed similar features	ANA+, anti-SSBLa+, and anti-RNP+. Thrombocytopenia	Multiple site	Large areas of interfollicular necrotizing inflammation with a prominent histiocytic population and admixed lymphocytic debris, but no neutrophils. Immunohistochemistry revealed that the interfollicular/ paracortical areas were populated predominantly by cytotoxic/CD8-positive T-cells	MCT-D+KFD	Dead
Szodoray P. (2008)	48	F	Symmetrical non-erosive polyarthritis of the small joints of the hands, swollen fingers and cold-induced Raynaud's phenomenon. Myalgia in the proximal lower and upper limb muscles. EMG proved myositis. Four years later fever, dyspnea, unproductive cough and bilateral hilar lymph adenomegaly	Elevated ESR, CRP, and CPK. ANA+, anti-RNP+ with the absence of other autoantibodies	Mediastinal	Non-necrotizing epithelioid granulomas	MCTD+ sarcoidosis	Alive
Szodoray P. (2008)	58	F	Pain in the small joints of the hands, fever, symmetrical polyarthritis involving the metacarpophalangeal and proximal interphalangeal joints, wrist, knees, proximal muscular pain, sclerodactyly and Raynaud's phenomenon. Arthritis and myositis, swelling of the bilateral metacarpophalangeal and proximal interphalangeal joints, severe unproductive cough, and fever. In both axillary regions lymph adenomegaly occurred	The ESR was 105 mm/h with mild leukopenia and mild anemia. ANA+, high anti-RNP with absence of other detectable autoantibodies and hypergammaglobulinemia	Mediastinal	Epithelioid granulomas	MCTD+ sarcoidosis	Alive
Yiannopoulos G. (2013)	47	F	Interstitial lung disease, symmetric polyarthritis, myositis with elevation of muscle enzymes with compatible electromyographic findings, Raynaud's phenomenon. Years after she developed arthritis in the small joints of her hands and atypical abdominal pain, multiple enlarged lymph nodes, with a diameter more than 3cm along the iliac vessels bilaterally	High titer anti-RNP accompanied by elevated serum indices of inflammation	Abdominal	Reactive lymphadenopathy with follicular hyperplasia	MCTD+RL	Alive
Karsulovic C. (2021)	28	M	Lung and cutaneous involvement by MCTD (synovitis, Raynaud's, and hand edema). He presented with mild COVID-19 with low-grade fever, sore throat, dry cough, and myalgias. After 3 weeks, he reconsulted with fevers, weight loss, cervical lymphadenopathies, and polyarthralgia. Multiple cervical and axillary lymph nodes ranging from 12 to 15 mm. Internal mammary and retro-pectoral lymph nodes ranging from 9 to 12mm. Perihepatic and iliac lymph nodes ranging from 15 to 16 mm	anti-RNP titers over 1: 1000, CRP ×3 times normal value ESR: 73 mm/hr	Cervical	Multiple lymphoid follicles with lymphoplasmacytic and histiocytic infiltrate. CD20 and CD3 reactive pattern, BCL2 reactive pattern	MCTD+ COVID-19 and RL	Alive
Erlij D. (2020)	51	F	Supraclavicular, axillary, mediastinal, and retroperitoneal lymph nodes. Absence of fatigue and B-symptoms	Normal ESR and LDH		FH	MCTD+RL	Alive
Guit GL. (1985)	19	F	Raynaud phenomenon and seropositive polyarthritis, disabling muscle weakness in the proximal muscles of the lower extremities and, to a lesser extent, of the upper extremities. Swelling over the small joints, fusiform thickening of the fingers, and tightness of the skin of the hands.	Increased CPK, aldolase, and creatine values, hypergammaglobulinemia, and ANA+, ENA+, and anti-RNP+.	Mediastinal	Nonspecific lymphoid reaction with no features of sarcoidosis or lymphoma.	MCTD+RL	Alive

Frayha RA. (1985)	26	F	Fever (up to 39°C) and 18 kg weight loss. Two years earlier she had migratory polyarthritis with swelling of the knees, wrists, PIP and MCP joints together with morning stiffness and Raynaud's phenomenon. Hyperpigmentation of the sun exposed areas of skin and loss of pliability of the digits gradually developed. Acro sclerosis, and puffiness of the dorsal aspect of both hands were evident. No telangiectasias or digital ulcers were present. A few small axillary and inguinal lymph nodes were identified. The spleen was 3 cm below the costal margin. The proximal muscles were weak, tender, and atrophic. CT scans revealed enlarged left para-aortic, and bilateral iliac lymph nodes. Hand radiographs showed no evidence of rheumatoid arthritis, but calcinosis cutis was present. She was also diagnosed with SjS.	Hemoglobin of 10.6 g/dl, ESR ranged between 47 and 100 mm/h. Elevated alkaline phosphatase to above twice the upper limit of normal. CPK was 763, LDH was 742, and aldolase was 33 2. C3 was depressed. ANA+, anti-SSARo+, and anti-RNP+. The ENA hemagglutination titer (RNase-sensitive) was 1:8192. Protein and immunoelectrophoresis demonstrated marked elevation of IgG without paraproteinemia	Para-aortic	The lymph nodes showed a spectrum of changes ranging from sinus histiocytosis to pseudo lymphoma. The latter changes were most manifest in the porta hepatis nodes. Their architecture was partially or totally effaced. Activated B lymphocytes, morphologically identical to immunoblasts were abundantly seen. Their increased number, large nucleoli, little cytoplasm, and frequent mitoses suggested malignancy. Other cells including plasma cells, eosinophils, and histiocytes were present.	MCTD+SjS+ RL	Alive
Maronesi Bagio T. (2025)	44	F	Lower limb weakness, accompanied by left lower limb paresthesia, asthenia, Raynaud's phenomenon, 6kg weight loss. Physical examination revealed microstomia, reduced facial expression marks, sclerodactyly, skin thickening in the upper limbs, muscle weakness in all limbs. PET/CT scans revealed right supraclavicular, subpectoral and axillary, upper and lower paratracheal, perihilar lung region bilaterally, distal end of the esophagus and retroperitoneal lymphadenopathies peripheral pulmonary opacities predominating in the lower lobes and the upper lobe of the left lung, associated with ground-glass opacities and thickening of the interlobular septa. She also had pericardial effusion, and pulmonary hypertension	Anti-RNP+, Anti-SSB+, RF+ and ANA+. Leukopenia, positive direct Coombs, CRP 66 mg/L, elevated CPK, aldolase, AST, LDH 960 U/L, total proteins 7.8 g/dl, albumin 3.1 g/dl	Cervical	Small lymph node with a distorted general architecture due to the absence of follicles. Lymphocytes of varying sizes, histiocytes and occasional eosinophils are observed, suggesting reactive lymph node enlargement	MCTD+RL	Alive
Bennet RM. (1980)	27	F	Raynaud's phenomenon followed by pain and swelling of PIP joints and knees and ankles. Over the course of the next 3 years she had transient episodes of pyrexia and developed a generalized lymphadenopathy	Hb, 13.9g/dl; WBC, 4,600/mm'; gamma globulins, 2.35 g/dl (N,1.7); ESR, 25 mm/hr; anti-RNP antibodies 1.6 x 10^6; dsDNA antibodies-; Sm antibodies-, CPK normal.	Axillary	FH	MCTD+RL	NA
Bennet RM. (1980)	47	F	Raynaud's phenomenon and intermittent arthralgias for some 20 years before admission for grand mal seizure. Active synovitis of the PIP and MCP joints, the wrists, and MTP joints; generalized lymphadenopathy; maculo-papular rash over arms and legs, and a cerebellar ataxia in the lower limbs. Poor peristalsis in distal esophagus	ESR 17 mm/h; γ-globulins 2.64 g/dL; RF negative; ANA speckled 1:4,000; anti-RNP high titer; anti-Sm/anti-dsDNA negative; C4 48 mg/dL; urinalysis normal; VDRL negative	Axillary	Area of infarction at the hilum involving both lymph node parenchyma and hilar fat. Several vessels were occluded by organizing thrombus with vessels at the margin of the infarcted area showing intimal proliferation. There was also histiocyte hyperplasia in follicles, paracortical areas, and sinusoids.	MCTD+RL	Alive

Abbreviations: ANA, antinuclear antibodies; anti-RNP, anti–ribonucleoprotein antibodies; anti-dsDNA, anti–double-stranded DNA antibodies; anti-Sm, anti-Smith antibodies; anti-SSA/Ro, anti–Sjögren's-syndrome-related antigen A antibodies; anti-SSB/La, anti–Sjögren's-syndrome-related antigen B antibodies; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; ENA, extractable nuclear antigen antibodies; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; RF, rheumatoid factor; IgG, immunoglobulin G; C3/C4, complement components 3/4; EMG, electromyography; CT, computed tomography; PET/CT, positron emission tomography/computed tomography; FH, follicular hyperplasia; KFD, Kikuchi–Fujimoto disease; MCTD, mixed connective tissue disease; SjS, Sjögren's syndrome; RL, reactive lymphadenitis; MCP, metacarpophalangeal; PIP, proximal interphalangeal; MTP, metatarsophalangeal; COVID-19, coronavirus disease 2019; FUP, follow-up.

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