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Mixed Connective Tissue Disease Associated with Other Autoimmune Diseases as Giant Cell Myocarditis, Vitiligo and Autoimmune Hemolytic Anemia, A Multiple Autoimmune Syndrome Impossible to Type, Revised Multiple Autoimmune Syndrome Classification Extended to Type 4 Needed. About Two Cases

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ABSTRACT

Introduction: *Multiple autoimmune syndrome (MAS) is defined by the presence of at least 3 autoimmune diseases in the same person. It is subdivided into 3 types. Mixed connective tissue disease (MCTD) associated to other autoimmune diseases is more and more reported and do not correspond with any type of MAS classification this is why we propose to revise multiple autoimmune syndrome classification extended to type 4 and for which we report two cases.*

Clinical observation: Patient 1: *An 18-year-old Malian female presented to the outpatient clinic with 3-months history of pruritic achromic skin patches, Gottron's papules, polyarthralgias and exertional dyspnea. Mixed connective tissue diseases associated with vitiligo and autoimmune hemolytic anemia was raised. The mixed connective tissue diseases associating systemic lupus erythematosus (EULAR/ACR 2019), rheumatoid arthritis with subcutaneous rheumatoid nodule (EULAR/ACR 2010), systemic scleroderma (EULAR/ACR 2013), and probable dermato-polymyositis (Bohan and Peter 1975) as well as the Kasukawa's criteria 1988 fulfilled was considered. Vitiligo of autoimmune origin was retained because of the clinical context and the immunological disorder in this case. The positivity of the direct coombs test in a context of hemolysis allowed us to rule in the diagnosis of autoimmune hemolytic anemia.*

Patient 2: *30-year-old nulligest woman with no past medical history presented to the internal medicine outpatient clinic because of a gangrene of the index finger and right thumb, ecchymotic lesions over the right hand, phenomenon of Raynaud, Gottron's papules and polyarthritis that started three months ago. Suspected giant Cell myocarditis associated to CMTD with left hand dry gangrene complicating probably the vasculiratis induced by connectivitis was suggested. Suspicion giant cell myocarditis was retained because of segmental dyskinesia and impaired systolic ejection function on cardiac Doppler ultrasound, ventricular tachycardia and left bundle branch block on ECG and heart failure syndrome in a context of co-diagnosis with several autoimmune diseases and markedly improvement of the left ventricular ejection fraction with co-administration of cardiologist'prescrition and disease-modifying antirheumatic drugs. Mixed connective tissue diseases associated with dry gangrene complicating probably the vasculitis induced by connectivitis was retained based on the Kasukawa 1988 criteria and the presence of dry gangrene with the absence of other contexts that could explain the vasculitis (normal lipidogram, absence of chronic infection, iatrogeny and delebile terrain). Thus, systemic lupus erythematosus was retained in front of (EULAR/ACR 2019); rheumatoid arthritis, (EULAR/ACR 2010); probable dermato-polymyositis (Bohan and Peter 1975), and scleroderma (EULAR/ACR 2013).*

Conclusion: *Both cases have some interesting aspects; firstly, MCTD associated with vitiligo, AHA and GCM is relatively rare and do not be occulted by Physicians who care MCTD patients, and secondly, MCTD alone or its related autoimmune diseases cannot be typed according to the current MAS classification. The limits of the current MAS classification would open the way to its revision through a systematic review and meta-analysis.*

Keywords
Multiple autoimmune syndrome, Mixed connective tissue diseases, Giant cell myocarditis, Vitiligo, Autoimmune hemolytic anemia.

Introduction
Multiple autoimmune syndrome (MAS) is the coexistence of three or more autoimmune diseases. Multiple autoimmne syndrome can be classified into three groups that correspond with the prevalence of their being associated with one another in patients with two autoimmune diseases [1,2]. About 25 percent of patients with autoimmune diseases have a tendency to develop additional autoimmune disorders [3].

Indeed, to understand immuno-genetic ancestral origin and common pathophysiological and clinical feature of some autoimmune disease groups like MAS could help to develop common therapeutic and diagnostic strategy for these autoimmune diseases. In addition, the occurrence of multiple autoimmune phenomena indicates the need for continued surveillance for the development of new autoimmune disease in predisposed patients [2].

However, there are some difficulties with this current multiple autoimmune syndrome classification [1] that was based on the prevalence of autoimmune disease associations. For example, the mixed connective tissue disease (MCTD) associated with other autoimmune diseases that is more and more reported [4-12]. MCTD is a distinct disease entity with mixed features of systemic lupus erythematosus, systemic sclerosis, myositis, and rheumatoid arthritis with high titers of antibodies to U1 ribonucleoprotein (U1RNP) [13]. Each type of MAS includes one or more components of MCTD, MAS Type 1 includes the polymyositis, MAS type 2 the scleroderma and rheumatoid arthritis, and MAS type 3 the systemic lupus erythematosus.

Revision of MAS classification, on the basis of systematic review and meta-analysis of exhaustive autoimmune disease association prevalence, could be necessary and could resulted to the proposition of MAS type 4 which could be a mixed connective tissue diseases associated with other autoimmune diseases of which we report two cases, firstly, MCTD associated with vitiligo and autoimmune hemolytic anemia, and secondly, suspected giant cell myocarditis associated to MCTD with left hand dry gangrene complicating suspected vasculitis induced by connectivitis.

Clinical Observation
Patient 1
An 18-year-old Malian female presented to the internal medicine outpatient clinic with 3-months history of pruritic achromic skin patches, Gottron's papules, polyarthralgia with arthritis and exertional dyspnea. There was intermittent, moderate to high intensity, and inflammatory feature of pain in several small and large joints associated with the morning stiffness as was left wrist and proximal interphalangeals joints swollen. The patient had also noticed a prolonged fever, and a decrease in appetite but she denied cough and chest pain. Her mother had an unspecified dermatosis. She had no medical History. The physical examination revealed a temperature of 38.1°C, a heart rate of 94 beats per minute, a respiratory rate of 28 cycles per minute, and a Body Index Mass (BMI) of 16.17 kilogram per square meter. The dermatological examination revealed bilateral and symmetrical achromic macular lesions over the forearms, trunk, neck, scalp and limbs; heliotropic eruptions over the face, Gottron's papules opposite the interphalangeal joints; dry, thickening, and induration skin over the fingers, hands, forearms and arms with pudgy fingers; painless, ulcerated, firm and mobile subcutaneous nodules on the right elbow; and alopecia (figure 1). Rheumatologic examination revealed swelling of the left wrist, pain in large and small joints in responses to the palpation and mobilization, amyotrophy and Tabouret sign was present. The breath sounds were heard with bibasilar fine crackles. The digestive examination noted a microstomy. The blood count showed a hemoglobin level of 8.1 g per deciliter, reticulocytes of 128170 per cubic millimeter, lymphocyte count of 801 per cubic millimeter, and blood white-cell count of 2888 cells per cubic millimeter. The hemolysis workup showed an unconjugated bilirubin level of 82 µmol per liter (normal range, 3.4 to 12.0 µmol per liter) and a haptoglobin

level of 0.08 g per liter (normal range, 0.5 to 2.2 g per liter). The inflammatory workup showed that the erythrocyte sedimentation rate (ESR) was 99 mm at the first hour (normal range, 0 to 29 millimeter) and the blood C-reactive protein level was 56.5 mg per liter (normal value, < to 6 mg per liter). The blood lactate dehydrogenase was 840 IU per liter (normal range, 105 to 333 IU per liter) and the blood creatinine phosphokinase level was 4645 U per liter (female normal range, 26 to 192 U per liter). A blood tests for antinuclear antibodies was positive at a titer of 1:1230 with speckled pattern and anti-Smith antibodies was weakly positive, rheumatoid factor was positive at 100 IU per milliliter, but anti-CCP antibody, anti-native DNA antibody, anti-Scl70 antibody and anti-Jo1 antibody were negative. Additional serologic testing for anti-U1-RNP antibody was positive and direct coombs test was positive. The spirometer test, performed before presentation, revealed a restrictive respiratory disorder in favor of parenchymal manifestations of scleroderma.

A diagnosis of mixed connective tissue diseases associated with vitiligo and autoimmune hemolytic anemia was raised.

The mixed connective tissue diseases associating systemic lupus erythematosus (EULAR/ACR 2019) [14] (table 1), rheumatoid arthritis with subcutaneous rheumatoid nodule (EULAR/ACR 2010) [15] (table 2), systemic scleroderma (EULAR/ACR 2013) [16] (table 3), and probable dermato-polymyositis (Bohan and Peter 1975) [17] (table 4) as well as the Kasukawa's criteria 1988 [18] fulfilled (table 5) was considered. Vitiligo of autoimmune origin was retained because of the clinical context and the immunological disorder in this case. The positivity of the direct coombs test in a context of hemolysis allowed us to rule in the diagnosis of autoimmune hemolytic anemia.

Treatment with prednisone at the dose of 1 mg per kilogram tapering courses was begun with adjuvant therapy. After ophthalmological examination, whithout contraindication, the hydroxychloroquine was added to corticoid. On three-month fellow-up visit, systemic condition disappeared and on nine-month fellow-up visit the vitiligo lesion had slightly improved and had completely resolved on 1-year follow-up visit.

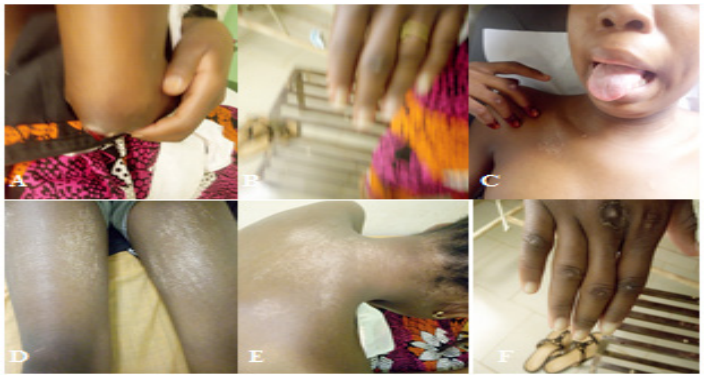


Figure 1: showing dermatological examination findings of the patient 1
A: Bleeding ulcerated subcutaneous nodule on the elbow
B: Proximal interphalangeal joints swollen
C: Microstomia observed at the opening of the mouth
D: Symmetrical and bilateral vitiligo lesion on the thighs
E: vitiligo lesions observed over the back, neck and scalp
F: Gottron's papules opposite the proximal interphalangeal joints

Patient 2

30-year-old nulligest woman with no past medical history presented to the internal medicine outpatient clinic because of a gangrene of the index finger and right thumb, ecchymotic lesions over the right hand, Raynaud' phenomenon, Gottron's papules and polyarthralgia that started three months ago. She also reported right knee and left wrist swelling and morning shiftiness, a decrease in appetite and prolonged fever. Three months before her presentation, she was diagnosed to the cardiology outpatient consultation with decompensated heart failure secondary of unspecified myocarditis revealed by palpitation, fatigue, dyspnea, grade 3 arterial hypertension , irregular heartbeat, tachycardia; a chest X-ray showing cardiomegaly; an ECG showing ventricular tachycardia and left heart block; a cardiac Doppler ultrasound showing segmental dyskinesia and an altered left ventricular ejection fraction with 40%; and an elevated ProBNP, ASAT, CPK and troponin level. She was followed up by cardiologists. Cardiologist's prescription includes bisoprolol (10 mg once daily), perindopril (10 mg once daily), and amlodipine (10 mg once daily). The evolution was marked by slight improvement of the left ventricular ejection fraction (LVEF) and the persistence of uncontrolled blood pressure and ventricular arrhythmia. On physical examination, the blood pressure was 170/120 mmHg, the heart rate was 100 beats per minute, the respiratory rate 28 cycles per minute, the temperature was 38.6°C and the Body Mass Index (BMI) was 19.58 kilogram per square meter. The dermatological examination noted pulpitis on the fingertips; Raynaud's phenomenon in the syncopal phase and in the recovery phase after cold exposure; dry gangrene of the right index finger and thumb with peri-lesional inflammatory signs; multiple ecchymotic lesions over the right hand; Grottron's papules; scarring lesions of prurigo disseminated to the body; thickening and induration skin especially over the fingers, hands, forearms, face, trunk and lower limb with Rodnan score at 41 points; dry skin with slightly pruritic and without scales; and alopecia. The digestive examination showed a decrease in the opening of the mouth. The rheumatological examination noted pain in several small and large joint with palpation and mobilization and a swelling of the wrists; an amyotrophy with a positive Tabouret sign.

The complete blood count showed a normocytic normochromic anemia (the hemoglobin level was 9.9 g per deciliter, the mean corpuscular volume was 92.4 femtoliter, and the mean corpuscular hemoglobin concentration was 28.2 picograms) with lymphopenia (lymphocytes, 1000 cells per cubic millimeter), neutropenia (neutrophils, 1050 cells per cubic millimeter) and thrombocytopenia (platelet count, 90 000 cells per millimeter). The hemolysis profile was normal. The inflammatory markers was elevated, the erythrocyte sedimentation rate at 65 millimeter at the first hour (normal range, 0 to 29 millimeter), and the blood C-reactive protein level at 87 mg per liter (normal value, < to 6 mg per liter). The blood lactate dehydrogenase was 755 IU per liter

(normal range, 105 to 333 IU per liter) and the blood creatinine phosphokinase level was 5015 U per liter (female normal range, 26 to 192 U per liter). The lipid profile was unremarkable. The immunological testing for anti-nuclear antibodies was elevated at 1: 1280 (titer on Hep2 cell, speckled fluorescence aspect), anti-native DNA antibodies was negative, anti-Smith antibodies positive, anti-U1 RNP antibodies positive. Rheumatoid factor was positive at 143 IU/ml but anti-CCP antibody was negative. The other autoantibodies, anti-Scl70 antibody, anti-SSA antibody, anti-SSB antibody, anti-Jo1 antibody and anti-centromere antibody were negative. Antiphospholipid antibodies were also negative. Heart-specific autoantibodies, anti-sarcolemma, anti-myolemma, and anti-fibrillar antibodies, were not performed. The infectious assessment was unremarkable. Skin biopsy was not performed. The doppler studies of the upper extremities showed no evidence of the thrombi but the angioscanner of the right upper extremity showed a deep venous thrombosis. Myocardial magnetic resonance imaging and scintigraphy, and endomyocardial biopsy were not performed.

A diagnosis of giant cell myocarditis associated to MCTD with left hand dry gangrene complicating suspected vasculitis induced by connectivitis was suggested.

The suspected giant cell myocarditis was considered because of the presence of segmental dyskinesia and impaired systolic ejection function on cardiac Doppler ultrasound, ventricular tachycardia and left bundle branch block on ECG and heart failure syndrome in a context of co-diagnosis with several autoimmune diseases and markedly improvement of the left ventricular ejection fraction when co-administration of cardiologist'prescrition and Disease-modifying antirheumatic drugs. Mixed connective tissue diseases associated with dry gangrene complicating suspected vasculitis induced by connectivitis was retained based on the Kasukawa 1988 criteria [18] (Table 1) and the presence of dry gangrene with the absence of other contexts that could explain the vasculitis (normal lipidogram, absence of chronic infection, iatrogeny and general debility context). Thus, systemic lupus erythematosus was retained in front of (EULAR/ACR 2019) [14] (Table 2);

Table 1: EULAR/ACR 2019 for the classification of systemic lupus erythematosus in our patients.

EULAR/ACR 2019 criterion	Patient 1	Patient 2
EULAR/ACR 2019 entry criterion Antibody antinuclear a titer at ≥1:18 on Hep cell or equivalent	Antinuclear antibody = 1 : 1230	Antinuclear antibody = 1 : 1280
EULAR/ACR 2019 additive criteria		
Clinical domain and criteria (Weight)		
Constitutional - Fever (2)	Temperature = 38,1°C	Temperature = 38,6°C
Hematologic - Leukopenia (3) - Thrombocytopenia (4) - Autoimmune hemolysis (4)	Leukopenia and autoimmune hemolysis found	Leucopenia, and thrombocytopenia found
Neuropsychiatric - Delirium (2) - Psychosis (3) - Seizure (5)	Not found	Not found
Mucocutaneous - Non-scarring alopecia (2) - Oral ulcers (2) - Subacute cutaneous or discoid lupus (4) - Acute cutaneous lupus (6)	Non-scarring alopecia found	Non-scarring alopecia found
Serosal - Pleural or pericardial effusion (5) - Acute pericarditis (6)	Not found	Not found
Musculoskeletal - Joint involvement (6)	Several small and large joints involved	Several small and large joints involved
Renal - Proteinuria > 0.5 g/24 H (4) - Renal biopsy class II or V lupus nephritis (8) - Renal biopsy class III or IV lupus nephritis (10)	Not found	Not found
Immunology domain and criteria (Weight)		
Antiphospholipid antibodies - Anticardiolipid antibodies OR - AntiBeta2GP1 antibodies OR - Lupus anticoagulant (2)	Not performed	Performed but not found
Complement proteins - Low C3 or low C4 (3) - Low and low C4 (4)	Not performed	Not performed
SLE-specific antibodies - Anti-dsDNA antibody OR - Anti-smith antibody (6)	Anti-smith antibody was positive	Anti-smith antibody was pasitive
Classify as systemic lupus erythematosus with a score of 10 or more if entry criterion fulfilled		

Table 2: EULAR/ACR 2010 RA for the classification of rheumatoid arthritis in our patients.

EULAR/ACR 2010 criterion	Patient 1	Patient 2
EULAR/ACR 2010 RA entry criterion - Definite swelling of at least one joint on clinical examination, for whom another diagnosis (e.g. SLE, PsA, gout) does not better account for the synovitis.	Left wrist and proximal interphalangeal joints swollen reported and found	Right knee and left wrist swollen reported ; left wrist swollen found
EULAR/ACR 2010 criteria (Score)		
Joint involvement - 1 large joint (0) - 2–10 large joints (1) - 1–3 small joints (large joints not counted) (2) - 4–10 small joints (large joints not counted) (3) - >10 joints including at least one small joint (5)	More than 10 joints with small joints	More than 10 joints with small joints
Serology *(at least one test needed for classification)* - Negative RF and negative ACPA (0) - Low positive RF or low positive ACPA (2) - High positive RF or high positive ACPA (3)	RF was positive ACPA was negative	RF was positive ACPA was negative
Acute-phase reactants *(at least one test needed for classification)* - Normal CRP and normal ESR (0) - Abnormal CRP or abnormal ESR (1)	CRP was elevated at 56.5 mg per liter 1 hour ESR was elevated at 99 millimeter	CRP was elevated at 87 mg per liter 1 hour ESR was elevated at 65 millimeter
Duration of symptoms - <6 weeks (0) - ≥6 weeks (1)	Three-month history of polyarthralgia reported	Three-month history of polyarthralgia reported
A total score of ≥ 6 is needed to classify a patient as having definite RA.		

Table 3: EULAR/ACR 2013 criteria for the classification of systemic sclerosis in our patients

EULAR/ACR 2013 criteria	Patient 1	Patient 2
EULAR/ACR *2013 entry criteria* - These criteria are applicable to any patient considered for inclusion in a SSc study - These criteria are not applied to: . Patients having a SSc-like disorders better explaining their manifestations, such as: nephogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host diseases, and diabetic cheiropathy. . Patients with skin thickening sparing the finger.	Patient did not present a SSc-like disorders better explaining their manifestations, She presented a skin thickening of the finger	Patient did not present a SSc-like disorders better explaining their manifestations, She presented a skin thickening of the finger
Items *(Wieght/Score)*		
- Skin thickening of the finger of both hands extending proximal to the metacarpophalageal joints (sufficient criterion) (9)	Dry, thickening, and induration skin over the fingers, hands, forearms and arms with pudgy fingers found	thickening and induration skin especially over the fingers, hands, forearms, face, trunk and lower limb with Rodnan score at 41 points
- Skin thickening of the fingers (only count the hightest score) . Puffy fingers (2) . Sclerodactyly of the finger (distal to MCP but proximal to the PIPS) (4)	Induration skin over the fingers found	Induration skin especially over the fingers found
- Finger tip lesions (only count the hightest score) . Digital tip ulcers (2) . Finger tip pitting scars (3)	Not found	Fingertip pitting scars (pulpitis on the fingertips) found
Telangiectasia (2)	Not found	Not found
Abnormal nailfold capillaries (2)		
Pulmonary arterial hypertension and /or interstitial lung disease (2)	Bibasilar fine crackles and interstitial lung disease, spirometer test disclosed parenchymal manifestations of scleroderma.	Not found
Raynaud's phenomena (3)	Not found	Raynaud's phenomenon in the syncopal phase and in the asphyxia phase after cold exposure found
Scleroderma related antibodies (any of anti-centromere, anti topoisomerase1, anti RNA polymerase III) (3)	Performed but not found	Performed but not found
Patients having a total score of 9 or more are being classified as having definite systemic sclerosis.		

rheumatoid arthritis, (EULAR/ACR 2010) [15] (Table 3); probable dermato-polymyositis (Bohan and Peter 1975) [17] (Table 4), and scleroderma (EULAR/ACR 2013) [16] (Table 5).

The treatment with prednisone at a dose of 1 mg per kilogram of body weight a day with 1-year tapering course associated with adjuvant treatments, methotrexate 7.5 mg a week associated with folic acid 5 mg with 15 mg a week, hydroxychloroquine 200 mg twice daily and analgesic drugs. Antithrombotic drug was administered with instruction to visit vascular surgery. The patient refuse proposed therapeutic option from vascular surgery. Cardiologist's prescription was continued.

On two months follow-up visit, general and cutaneous signs markedly improved, LVEF normalized, but uncontrolled blood pressure and ventricular arrhythmia persisted. The patient was referred again for left hand dry gangrene complicating suspected vasculiratis induced by connectivitis for vascular surgery management. The blood pressure and ventricular arrhythmia had slightly improved on six months follow-up visit. Three month later, the patient was considered lost to follow-up.

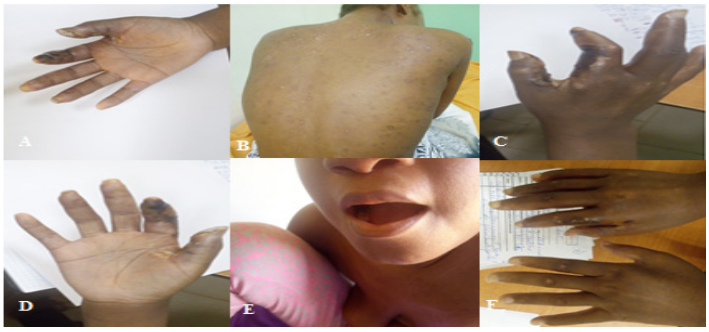
Table 4: Bohan and Peter's criteria 1975 for the classification of dermatomyositis (DM) in our patients.

Bohan and Peter's criteria 1975	**Patient 1**	**Patient 2**
Exclusion criteria: central or peripheral neurologic diseases, muscular dystrophies, granulomatous and infectious myositis, metabolic and endocrine myopathies, and myasthenia gravis.	Exclusion criteria discussed	Exclusion criteria discussed
Items		
Symmetric proximal muscle weakness determined by physical examination	Amyotrophy with a positive Tabouret sign	Amyotrophy with a positive Tabouret sign
Elevation of serum skeletal muscle enzymes, including creatine kinase, aldolase, serum glutamate oxaloacetate and pyruvate transaminases, lactate dehydrogenase	The blood lactate dehydrogenase was elevated at 840 IU per liter and the blood creatinine phosphokinase level was elevated at 4645 U per liter	The blood lactate dehydrogenase was elevated at 755 IU per liter and the blood creatinine phosphokinase level was elevated 5015 U per liter
The **electromyographic triad** of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges	Not performed	Not performed
Muscle biopsy abnormalities of degeneration, regeneration, necrosis, phagocytosis, and an interstitial mononuclear infiltrate	Not performed	Not performed
Typical skin rash of DM, including a heliotrope rash and Gottron's sign/papules	Heliotropic eruptions over the face and Gottron's papules found	Gottron's papules found
The diagnosis of DM is considered definite, probable and possible when skin rash is associated with 3, 2 or 1 muscular criteria		

Table 5: Kasukawa Criteria 1987 for mixed connective tissue disease in our patients.

Kasukawa Criteria 1987	**Patient 1**	**Patient 2**
A. Common symptoms 1. Raynaud's phenomenon 2. Swollen fingers or hands	Swollen hand found	Raynaud's phenomenon swollen hand found
B. Anti-snRNP antibody positive	Anti-U1 RNP was positive	Anti-U1 RNP was positive
C. Mixed symptoms **1. SLE-like findings** a. Polyarthritis b. Lymphadenopathy c. Facial erythema d. Pericarditis or pleuritis e. Leuko- or thrombocytopenia **2. SSc-like findings** a. Sclerodactyly b. Pulmonary fibrosis, restrictive changes of lung, or reduced diffusion capacity c. Hypomotility or dilatation of esophagus **3. PM-like findings** a. Muscle weakness b. Elevated serum levels of muscle enzymes (CPK) c. Myogenic pattern on EMG	Left wrist and proximal interphalangeal joints swollen with polyarthralgia, heliotropic eruptions over the face and leukocytopenia found Sclerodactyly and pulmonary restrictive changes of lung found Amyotrophy with a positive Tabouret sign and the blood creatinine phosphokinase level was elevated at 4645 U per liter	Left knee and right wrist swollen with polyarthralgia and leuko- or thrombocytopenia found Sclerodactyly found Amyotrophy with a positive Tabouret sign and the blood creatinine phosphokinase level was elevated at 5015 U per liter
At least 1 of the 2 common symptoms plus positive for anti-snRNP plus 1 or more of the mixed symptoms in at least 2 of the 3 disease categories.		

Figure 2: showing dermatological examination findings of the patient 2
A: Dry gangrene of the right index finger and thumb with peri-lesional inflammatory signs.



B: Scarring lesions of prurigo disseminated on the back.
C: Raynaud's phenomenon in the recovery phase after the asphyxia phase.
D: Raynaud's phenomenon in the syncopal phase after cold exposure.
E: Microstomia observed at the opening of the mouth.
F: Gottron's papules opposite the proximal interphalangeal joints.

Discussion

This case report describes the onset MCTD associated with other autoimmune diseases in our two patients, such MTCD associated with vitiligo and autoimmune hemolytic anemia revealed by pruritic achromic skin patches, Gottron's papules, polyarthralgia with arthritis and exertional dyspnea in the patient 1, and suspected giant cell myocarditis associated to MCTD with left hand dry gangrene complicating suspected vasculitis induced by connectivitis by a gangrene of the index finger and right thumb, ecchymotic lesions over the right hand, Raynaud' phenomenon, Gottron's papules and polyarthralgia. In both cases, MTCD and its components diagnosis was made with appropriate classification criteria [14-18]. Despite the six autoimmune conditions diagnosed in-patient 1 et the five in patient 2 which are all the MAS components, it is impossible to type them according to current MAS classification [1].

The incidence of adult-onset MCTD in Norway during the period from 1996 to 2005 was 2.1 per million per year. In addition, the female to male ratio was 3.3 and the mean age at diagnosis of adult-onset MCTD was 37.9 years [19]. The clinical features of patients with MCTD vary and include those found in systemic lupus erythematosus, systemic sclerosis, polymyositis and occasionally rheumatoid arthritis. The frequency of each clinical findings differ slightly depending on the race of the patients studied and on the diagnostic criteria used. The present case is reported in two young women with clinical polymorphism presentation.

Patient 1 presented MTCD associated to vitiligo and autoimmune hemolytic anemia. Vitiligo is a chronic autoimmune disorder that causes patches of skin to lose pigment or color. This happens when melanocytes are attacked and destroyed, causing the skin to turn a milky-white color. In vitiligo, the white patches usually appear symmetrically on both sides of your body, such as on both hands or both knees. It is known that people with vitiligo may be more likely to develop other autoimmune disorders as well [20]. In our patient 1, the dermatological examination revealed bilateral and symmetrical achromic macular lesions over the forearms, trunk, neck, scalp and limbs.

Disease-associated autoimmune hemolytic anemia is a decompensated acquired hemolysis caused by the host's immune system acting against its own red cell antigens. The diagnosis of autoimmune hemolytic anemia can be made with a stepwise approach that aims to identify laboratory and clinical evidence of hemolysis and then determine the immune nature of hemolysis with the direct anti-globulin test [21]. A normocytic anemia, raised reticulocyte count, raised unconjugated bilirubin, reduced haptoglobin positive direct Coombs test with had led to rule in the diagnosis of autoimmune hemolytic anemia in our patient 1. The common confounder diseases should be rule out such G6PD, thalassemia, and sickle cell-disease. Anamnesis reported no history of thalassemia, sickle cell-disease in our patient 1.

Patient 2 presented suspected giant cell myocarditis associated to CMTD with left hand dry gangrene complicating suspected vasculitis induced by connectivitis.

Giant cell myocarditis is a rare cardiovascular disorder that occurs for unknown reasons (idiopathic). It is characterized by inflammation of the heart muscle (myocardium), a condition referred to as myocarditis. Giant cell myocarditis occurs primarily in previously healthy adults, although it is frequently associated with various systemic diseases, primarily of autoimmune causes. A diagnosis of giant cell myocarditis is made by biopsy of heart tissue. A biopsy is a test in which small tissue sample is surgically removed and studied microscopically [22,23]. The suspected giant cell myocarditis was considered in patient 2 because of the presence of segmental dyskinesia and impaired systolic ejection function on cardiac Doppler ultrasound, ventricular tachycardia and left bundle branch block on ECG and heart failure syndrome in a context of co-diagnosis with several autoimmune diseases and markedly improvement of the left ventricular ejection fraction when co-administration of cardiologist'prescrition and Disease-modifying antirheumatic drugs.

Is it possible to type MCTD with related autoimmune diseases according to current MAS classification [1]?

The idea of MAS issued by Humbert and Dupond in 1988 which allowed to explore the epidemiological and pathogenic relationship of some associated autoimmune disease of which 3 types were distinguished. However, this classification does not allow to type some autoimmune diseases, although they are components of MAS and their association is more and more prevalent and reported. This is the case of MCTD alone or associated with other autoimmune diseases. Indeed, MCTD associated with autoimmune hemolytic anemia [6,10], vitiligo [12], Grave's disease [8], autoimmune hepatitis [11], thrombotic thrombocytopenic purpura [4,9,10], Sjögren's syndrome [5,11], MPO-ANCA-positive Polyangiitis [7] had been reported. Further MCTD's associated or related diseases should be more explore. We know that, each type of MAS includes one or more components of MCTD, MAS Type 1 includes the polymyositis, MAS type 2 the scleroderma and rheumatoid

arthritis, and MAS type 3 the systemic lupus erythematosus.

In perspective, revision of MAS classification, on the basis of systematic review and meta-analysis of exhaustive autoimmune disease association prevalence, could be necessary and could resulted to the proposition of MAS type 4 which could be a mixed connective tissue diseases associated with other autoimmune diseases.

Conclusion

Both cases have some interesting aspects; firstly, MCTD associated with vitiligo, AHA and GCM is relatively rare and do not be occulted by Physicians who care MCTD patients, and secondly, MCTD alone or its related autoimmune diseases cannot be typed according to the current MAS classification. The limits of the current MAS classification would open the way to its revision through a systematic review and meta-analysis.

References

1. Humbert P and Dupond JL. [Multiple autoimmune syndromes]. Ann Med Interne. 1988; 139: 159-168.
2. Cojocaru M, Cojocaru IM, Silosi I. Multiple autoimmune syndrome. A Journal of Clinical Medicine. 2010; 5: 132-134.
3. Mohan MP, Ramesh TC. Multiple autoimmune syndrome. Indian J Dermatol Venerol Leprol. 2003; 69: 298-299.
4. Filho JTDS, Barros PV, Paes da Silva AMYR, et al. Thrombotic Thrombocytopenic Purpura Associated with Mixed Connective Tissue Disease: A Case Report. Case Reports in Medicine. 2011; 2011: 953890.
5. Gupta V and Kaeley N. Sjögren syndrome and mixed connective tissue disease. In: Vasudevan B and Verma R, Eds. Dermatological Emargencies. 1st Edition. 2019; 7.
6. Kelkar AH, Shah AA, Yong SL, et al. An unusual association between hemophagocytic lymphohistiocytosis, mixed connective tissue disease, and autoimmune hemolytic anemia. A case report Medicine. 2017; 96: 28.
7. Kitaura K, Miyagawa T, Asano K, et al. Mixed Connective Tissue Disease Associated with MPO-ANCA-positive Polyangiitis. Internal Medicine. 2006; 1177-1182.
8. Kozanolu ME, lke Coflkun Benliday, Sert M. A Case of Mixed Connective Tissue Disease Associated with Graves' Disease. Rheumatism. 2008; 23: 100-112.
9. Momin MAB, Prusty BSK, Reddy A. Thrombotic Thrombocytopenic Purpura with Mixed Connective Tissue Disease - Non-immune Hemolytic Anemia with Autoimmune Disease - Rare Case Report. J Bangladesh Coll Phys Surg. 2020; 38: 46-48.
10. Talesnik EG, Taboada HL, Rivero SD, et al. Autoimmune anemia and thrombocytopenia in Mixed connective tissue disease. Revista Chilena de Pediatria. 54: 101-104.
11. Wada T, Motoo Y, Ohmizo R, et al. Association of Mixed connective tissue disease, Sjogren's syndrome and autoimmune hepatitis. Jpn J Med. 1991; 30: 278-280.
12. Won SH, Shin K, Kim WI, et al. A Case of 'Salt and Pepper Appearance of the Skin' in Mixed Connective Tissue Disease. Korean J Dermatol. 2020; 58: 423-426.
13. Sharp GC, Irvin WS, Tan EM, et al. 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; 52: 148-159.
14. Aringer M, Costenbader KH, Daikh DI, et al. 2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019; 71: 1400-1412.
15. Kay J and Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology. 2012; 51: 5-9.
16. Hoogen FVD, Khanna D, Fransen J, et al. Classification Criteria for Systemic Sclerosis: An ACR-EULAR Collaborative Initiative. Arthritis Rheum. 2013; 65: 2737-2747.
17. Bohan A and Peter JB. Diagnostic criteria for dermatomyositis (DM). N Engl J Med. 1975; 292: 344-347.
18. Kasukawa R, Tojo T, Miyawaki S, et al. Preliminary diagnostic criteria for classification of mixed connective tissue disease: In: Kasukawa R, Sharp GC (eds). Mixed Connective Tissue Disease and Antinuclear Antibodies. Elsevier: Amsterdam. 1987; 41-47.
19. Gunnarsson R, Molberg O, Gilboe I, et al. PAHNOR1 Study Group. The prevalence and incidence of mixed connective tissue disease: a national multicentre survey of Norwegian patients. Ann Rheum Dis. 2011; 70: 1047-1051.
20. National Institute of Arthritis and Musculoskeletal and Skin diseases. Overview of vitiligo. [Retrieved october 31st 2022]. Available from: file:///C:/Users/USER/Downloads/Vitiligo%20en.pdf
21. Hill A and Hill QA. Autoimmune hemolytic anemia. Hematologia. 2018; 381-389.
22. Mayo Clinic. NORD's Rare Diseases database. Giant Cell Myocarditis. [Retrieved October 10th 2022]. Available from: https://rarediseases.org/rare-diseases/giant-cell-myocarditis/
23. Cooper LT, Berry GJ, AND Shabetai R, et al. For the multicenter giant cell myocarditis study group investigators. Idiopathic giant-cell myocarditis-natural history and treatment. N Engl J Med. 1997; 336: 1860-1866.