Think before: a guide to early diagnosis of pulmonary hypertension in patients with connective tissue diseases and vice versa

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Summary

Connective Tissue Diseases (CTDs) is a group of autoimmune disorders with common clinical and serological characteristics. Among them, Systemic sclerosis (SSc) is the disease most often associated with Pulmonary Arterial Hypertension (PAH), which is often diagnosed with delay for the unspecific symptomatology. A delayed diagnosis of PAH in patients with SSc may affect prognosis, but also a missed recognition of CTD in patients with PAH may be detrimental for clinical management.
This statement produced by a working group made up of rheumatologists and pneumologists has the objectives to suggest items useful for the identification, diagnosis and classification of CTDs in cases of already identified pulmonary disease and how to differentiate signs and symptoms arising respectively from parenchymal and vascular diseases in order to define a set of proposed recommendations on which consensus may be reached for their application in clinical practice.

KEY WORDS: pulmonary artery hypertension; connective tissue diseases; early diagnosis; interstitial lung diseases; systemic sclerosis.

Introduction

The connective tissue diseases (CTDs) are a group of autoimmune disorders that share a common clinical and serological substrate. They can affect the internal organs (respiratory, cardiovascular, digestive and genito-urinary systems) and have different patterns of evolution and prognosis. Examples include systemic lupus erythematosus (SLE), Sjögren syndrome (SS), systemic sclerosis (SSc), poly/dermatomyositis, and mixed connective tissue disease (MCTD).
Of the various clinical manifestations of CTDs, pulmonary hypertension (PH) is undoubtedly a major focus of attention, even though its prevalence and aetiology can vary. Because of the multi-organ nature of the disease, patients affected by CTDs may present different forms of PH, which can be classified into different groups according to the international guidelines.

Systematic echocardiographic screening for PAH in patients with SSc allows early treatment of PAH and has been shown to improve survival, probably by ensuring more timely specific treatment.

Pulmonary arterial hypertension (PAH) is a specific haemodynamic condition found in different diseases that are characterised by progressive vascular remodeling of the pulmonary arteries, leading to increased pulmonary vascular resistance and increased pressure in the pulmonary circulation, and right ventricular overload and, ultimately, failure. The diagnosis is confirmed by the results of right heart catheterisation, which must show a raised resting mean pulmonary artery pressure (mPAP) value of > 25 mmHg and a capillary wedge pressure less than 15 mmHg.
These criteria have to be present in order for PH to be classified in the Nice "Group I", in which the adoption of a therapeutic strategy based on the use of endothelin-1 receptor inhibitors, phosphodiesterase-5 inhibitors, and prostacyclins (generically defined as vasoactive drugs) has been recognised to be useful. However, the diagnosis and differentiation of the various forms is not easy as many patients with CTDs can present both in-

terstitial lung disease (i.e. a diffuse parenchymal disease with a variously fibrosing and progressive trend) and pulmonary vascular disease, which are classified differently in relation to the condition of PH and require a different drug treatment. Furthermore, it is not unusual for these two forms to coexist.

The treatment, and subsequent prognosis, also vary in relation to the patient's functional class (1), defined according to the scheme proposed by the WHO in which progression from class I to IV denotes a progressive worsening of the symptoms. The latter reflects a clinical situation which, in turn, depends on different pathophysiological mechanisms that are associated, obviously, with different prognoses.

The estimated prevalence of PAH, on the basis of data from French (2) and Scottish (3) registries, stands at between 25 and 50 patients per million, including both the primary forms and the conditions associated with PAH, which include the CTDs; in Italy, the overall prevalence is thought to correspond to a population of between 1500 and 2500 patients.

A diagnosis of PAH often carries the added burden of a not inconsiderable diagnostic delay. Because the symptoms are entirely non-specific and go undetected for a long time, patients tend to reach specialised reference centres late: this is the main reason why around 75% of patients do not receive a diagnosis, appropriate treatment and correct follow-up until they are already in an advanced functional class (WHO III - IV). Moreover, in the connective tissue disease-associated forms (PAH-CTDs), prevalence and survival are closely related to the type of associated autoimmune manifestation and vary significantly. SSc is undoubtedly among the CTDs most frequently associated with PAH, as shown by numerous reports in the literature (2): the association was present in up to 76% of the cases reported by the French registry, and had an estimated prevalence of between 7 and 12% of the overall scleroderma population (4, 5). Untreated patients show an estimated five-year survival rate of 10%, compared with 80% in patients with SSc and no associated PAH (6), which places PAH among the main and most severe complications of SSc. As expected from the study of other Group 1 forms, this figure changes in relation to functional class at the time of diagnosis or start of treatment with vasoactive drugs, being more favourable in subjects belonging to a better functional class (7). Nevertheless, there are, to date, no studies specifically designed to evaluate whether therapy started early may in itself have a positive influence on long-term survival.

The definition of a screening process (clinical and laboratory) able to identify, early on, which patients with CTDs are at risk of developing PAH, or to detect in a patient with PAH a previously unrecognised CTD, would certainly constitute a response to the need for early diagnosis, which is the only approach that, through an equally early targeted therapy, could – if not in the long term at least for a reasonable period – allow improvements in the quality of life and survival of these patients.

Aims of the present document

The main aims of the present statement are to:

- Provide essential parameters for identifying, diagnosing and classifying a CTD in a patient with pulmonary disease that has already been identified, diagnosed and classified
- Highlight the critical aspects and problems relating to the classification and identification of CTDs in patients with pulmonary disease
- Differentiate signs and symptoms deriving, respectively, from the vascular and parenchymal disease
- Develop recommendations and identify diagnostic pathways to be transformed into flowcharts for use in daily clinical practice.

A targeted treatment of PAH implies the early recognition of a possibly associated CTD.

Methods

A scientific board comprising 4 expert rheumatologists and 4 expert pulmonologists analysed current knowledge on the management of CTDs and PAH and pulmonary complications, taking into account the literature evidence and the guidelines on pulmonary hypertension. Thus, literature data and guidelines were used to draw up a list of elements that should be evaluated in patients presenting with pulmonary manifestations known to show possible associations with rheumatological diseases, both for follow-up purposes and for the purpose of developing recommendations to be transformed into a flowchart, on which to reach a consensus, for use in clinical practice.

Dyspnea should be evaluated with extreme care in any patient with CTD, preferably using a validated questionnaire.

It thus proved possible to define early signs/symptoms to be taken into account in daily clinical practice in order to simplify the approach to the problem, to make it homogeneous, and extend it to all centres (both pneumology and rheumatology centres) involved in the management of patients with CTDs with possible pulmonary involvement.

Clinical recommendations

The earlier PAH is diagnosed in CTD, the more effectively it can be treated, even though PAH, in any case, worsens the prognosis of the patient with CTD. Vice versa, patients with PAH should be always suspected for having an unknown CTD. For PAH to be diagnosed early, it is essential that the physician, in the presence of suggestive or indicative symptoms, recognises it as a possibility. Exertional dyspnoea, sometimes reported in terms of fatigue or asthenia, is usually the presenting symptom. This symptom is shared by forms of diffuse infiltrative pulmonary disease that can be associated with CTD, or sometimes precede a diagnosis of CTD. The differential diagnosis is therefore crucial and demands collaboration between the different specialists involved (rheumatologist, pulmonologist, cardiologist).

Table 1 shows the symptoms, signs, and laboratory and instrumental features of the patient with interstitial lung disease and/or pulmonary vascular disease that can simplify the approach to the early diagnosis and prompt

Table 1 - Clinical signs for identifying CTD.

Cutaneous signs	**Vascular signs**	**Signs involving the mouth and eyes**
• Scleroedema	• Raynaud's phenomenon	• Oral aphthae
• Skin sclerosis	• Digital ischaemic lesions	• Uveitis
• Purpura	• Telangiectasias	• Conjunctivitis
• Skin erythema	• Purpura	• Xerophthalmia
• Digital oedema	• Abdominal angina	• Xerostomia

Miscellaneous	**Laboratory findings**
Arthritis	Anti-mitochondrial antibodies and Reynolds syndrome
Pericarditis	Antinuclear antibodies (ANA)
Abdominal pain	Anti-ENA antibodies
	Anti-DNA antibodies
	Hypocomplementaemia
	Leukothrombocytopenia

suspicion of, or confirm, the presence of systemic autoimmune disease. It should be noted that, in these patients, pulse oximetry measurements during the walking test will often need to be recorded using ear or forehead probes. This is because of the bias (linked to possible presence of digital vascular disease) that can arise if the more usual finger probes are used.

Table 2 instead shows the signs that have been deemed risk factors whose presence should cause the clinician to suspect that a case of CTD is evolving into a form of PAH. From a clinical point of view it is crucially important to reconstruct the patient's medical history, focusing particularly on dyspnoea and its most common causes.

Dyspnoea, as already indicated, is the most frequent clinical symptom in CTD (found in 82% of SSc patients who develop PAH). Dyspnoea should be evaluated with extreme care using a validated questionnaire such as the standardised one (Table 3) recently proposed by a multidisciplinary group in Paris (6).

Echocardiography is the instrumental screening test capable of raising, early on, the suspicion of PAH in a patient with CTD. However, this examination can give estimated systolic pulmonary artery pressure (sPAP) values varying by as much as 20mmHg compared to real values and must always be confirmed by right heart catheterisation (Figure 1). Systematic echocardiographic screening allows early treatment of PAH and has been shown to be effective for ensuring more timely treatment of patients affected by SSc, with the possibility of impacting on their long-term survival too (8, 9).

In addition to evaluating dyspnoea and its evolution, it is also necessary to consider other symptoms in order to promptly detect a possible worsening of a patient's pulmonary disease-related clinical conditions (Table 4). Medical history and periodic monitoring of a patient's symptoms can be an easy and also useful approach to adopt.

Asking the patient a series of simple questions can be enough to collect the information necessary to understand whether or not there is pulmonary involvement and whether the patient is stable or, instead showing a worsening of his/her conditions (Table 5).

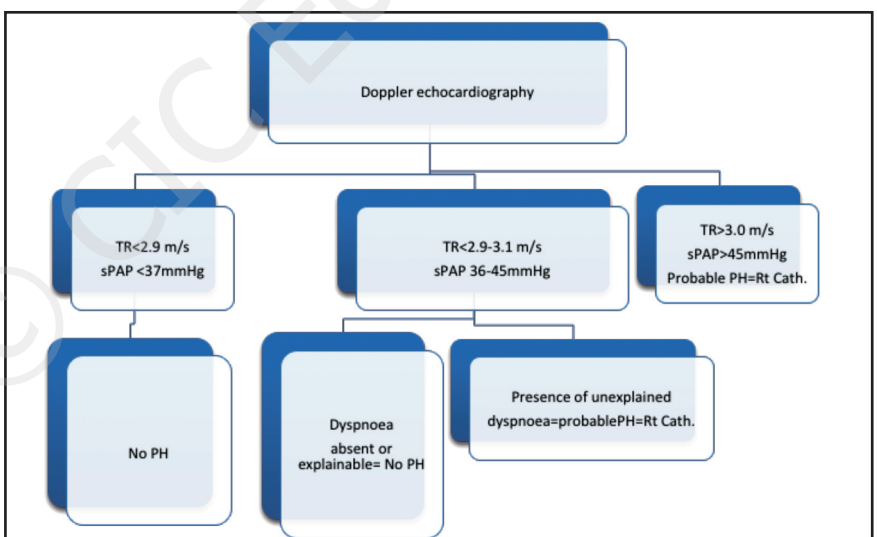
The non-invasive approach to early and differential diagnosis can be based not only on careful evaluation of signs and symptoms, particularly the emergence or worsening of dyspnoea, but also on assessment of the

Table 2 - Risk factors that should prompt suspicion of an evolution towards PAH.

• SSc	• Disease duration >10 years
• Raynaud's phenomenon for > 3 years;	• Age > 50 years
• Skin fibrosis progressively involving the hands, forearms, face, legs, feet	• Female gender
	• Number of teleangiectasias present for more than 10 years
• Gastrointestinal involvement	• Evolution of the capillaroscopic pattern towards a late pattern characterised by decreased capillary density
• Bone and joint involvement (myalgia, asthenia, arthralgia)	• Evolution of WHO class I into class II and III
• Anti-topoisomerase, anti-RNA polymerase, anti-centromere (ACA) antibodies	• DLco < 80% with normal FVC and HRCT

Table 3 - Questionnaire for evaluating dyspnoea in relation to functional class.

NYHA-WHO IV		YES	NO
1	Do you feel breathless when resting?	☐	☐
2	Can you get dressed without having to stop?	☐	☐
3	Can you take a shower without having to stop?	☐	☐
4	Do you get breathless walking around the house?	☐	☐
5	Can you walk a distance of 50 metres on level ground?	☐	☐
NYHA-WHO III			
6	Do you get breathless when climbing a flight of stairs (8 steps) or walking less than 100 metres at a normal pace?	☐	☐
7	Do you get breathless doing housework (making the bed, sweeping the floor, hanging out washing, cleaning the windows) or during leisure activities (shopping, pushing a supermarket trolley, playing bowls, playing golf, mowing the grass)	☐	☐
NYHA-WHO II			
8	Do you get short of breath going up two flights of stairs or up a hill?	☐	☐
9	Do you get short of breath when walking fast, gardening, or dancing slowly?	☐	☐
NYHA-WHO I			
10	Do you get short of breath doing demanding physical activities (running, skiing, cycling, climbing two flights of stairs carrying a child in your arms?	☐	☐



Legend: TR= tricuspid regurgitation flow velocity; sPAP= systolic pulmonary artery pressure; Rt Cath.= right heart catheterisation; PH= pulmonary hypertension.

Figure 1 - Echocardiographic screening: decision-making flow chart.

Table 4 - Clinical signs that may suggest a worsening of the conditions of a patient with CTD and PAH.

- Dyspnoea initially at rest and then worsening	- Pleural effusion	- Syncope
- Non-productive cough	- Chest pain	- Muscular weakness and fatigue
	- Reduced DLco (may indicate ILD, or PAH or both)	- Peripheral oedema

Table 5 - Questions to be put to the CTD patient periodically.

• Do you suffer from fatigue (asthenia)?	• Do you get short of breath? At rest? On exertion?
• Do you have any peripheral edema*?*	• Is your shortness of breath getting worse?
• Do you have any chest pain?	• Do you have pleural effusion?
• Do you suffer from syncope (fainting)?	• Have you had a spirometry test?
• Are you older than 50?	• Have you ever seen a lung specialist?

diffusing capacity of the lungs for carbon monoxide (DLco) and N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP) levels.

Frequency of respiratory involvement is not equal in the various forms of CTD. A defined diagnosis is important to be obtained because of the prognostic and therapeutic implications.

It is important to point out that BNP and NT-proBNP levels are indicators of general myocardial suffering and they are often raised in SSc-PAH patients. They are useful in clinical practice, even though they can be normal in the early stage of PAH, or altered in the absence of PAH as a result of left ventricular diseases, which, moreover, are not uncommon in SSc. There are also other instrumental examinations, in addition to echocardiography, that are useful in the differential diagnosis (Table 6), such as high-resolution CT scans.

Data on the usefulness of bronchoscopy with bronchioloalveolar lavage (BAL) and possibly transbronchial lung biopsy (TBB) in the differential diagnosis and assessment of disease activity are conflicting; conversely the value of these methods for identifying complications (infections, malignancies, etc.) is unanimously acknowledged.

In some patients with CTD, differential diagnosis can be complicated by the coexistence of PAH and interstitial involvement (diffuse infiltrative pulmonary disease), leading to the need of a multidisciplinary approach to better establish the optimal management and treatment (10).

The various forms of interstitial lung disease occur with varying frequency in patients with collagen diseases (CTDs), showing different radiological disease patterns associated with different prognoses (Table 7). A defined diagnosis is important to be obtained because of the prognostic and therapeutic implications.

All the classic patterns of interstitial lung disease occurring in patients with CTDs are characterised, with respect to the corresponding idiopathic forms, by a **greater degree of inflammation.** Increased inflammation can sometimes occur in the idiopathic forms of PH, too, in which case it is associated with a better prognosis. In RA, the presence of the **UIP pattern is a negative prognostic factor** that has a negative impact on quality of life (respiratory failure) and survival. A **UIP-like form secondary to RA** is nevertheless **less aggressive than idiopathic UIP** and responds better to treatment. **This same** pattern is also seen with in the **other forms** of CTD.

Connective tissue diseases should alway be considered in presence of a diffuse lung parenchymal disease, and this awareness could be crucial from both diagnostic and therapeutic points of view. To facilitate the readers to check this availability, Table 8 shows symptoms, signs, laboratory and instrumental findings suggestive for systemic autoimmune disease. Table 9 lists the main connective tissue diseases and their signs and symptoms.

In conclusion, both pulmonologists and rheumatologists must be suspicious for early detection of CTDs in patients with PAH, and vice versa. For the optimal management of patients with complex and uncommon diseases, like PAH and CTDs, a multidisciplinary and dedicated setting is strongly suggested.

Table 6 - Laboratory tests/instrumental examinations to perform if pulmonary involvement is suspected.

- BNP/NTpro BNP	**Echocardiography**
- Pulmonary function tests (global spirometry, cardiopulmonary exercise test)	High-resolution CT
- ECG	Bronchoscopy with BAL* and possibly TBB°
- DLco	

**BAL = bronchioloalveolar lavage*

°TBB = transbronchial lung biopsy

Table 7 - Frequency of respiratory involvement in the various forms of CTD.

CTD ⇒	SLE	RA	SSc	PM/DM	SJ	MCTD
Pattern ⇓						
UIP	+	++	++	++	+	++
NSIP	+	+	++++	++++	+	+++
DAD	++	+	+	+	…	…
OP	+	…	+	++	+	…
LIP	…	…	…	…	+++	+
DAH	+++	…	…	…	…	…
Bronchopathy	…	++	…	…	++	…

SLE = systemic lupus erythematosus, RA = rheumatoid arthritis, SSc = systemic sclerosis, PM/DM = poly/dermatomyositis, SJ = Sjögren syndrome, MCTD= mixed connective tissue disease, UIP = usual interstitial pneumonia, NSIP = nonspecific interstitial pneumonia,
DAD = diffuse alveolar damage, COP = organising pneumonia, LIP = lymphocytic interstitial pneumonia,
DAH = diffuse alveolar haemorrhage.

Table 8 - Symptoms, signs, and laboratory and instrumental findings in a patient with interstitial lung disease and/or Pulmonary vascular disease that prompt suspicion of, or confirm, the presence of systemic autoimmune disease. (*To be continued)*

Oral aphthae	Lesions / breaks in the oral mucosa, located on the hard or soft palate, asymptomatic or very painful.
Abdominal angina	Acute or chronic intestinal ischaemia, due to a gradual decrease in blood flow to the small intestine, caused by arterial disease affecting the mesenteric circulation. The pain initially occurs when demand for blood to the visceral organs is highest, typically after meals. It has a dull, cramping quality and is felt in mid abdomen; it arises between 15 and 30 minutes after eating and lasts a few hours before receding spontaneously.
Anti-ENA antibodies	These are autoantibodies directed against specific antigens present in the nucleus and extractable from the nucleus (ENA: extractable nuclear antigen). ELISA or immunoblotting tests are currently used for their determination. The correct approach is usually initial screening followed by determination of autoantibody specificities (SSA, SSB, RNP, Sm, Scl70, Jo-1). This is usually a second-level examination, carried out in patients positive for ANA. There are, however, instances in which patients can have a positive ENA (SSA in particular) but a negative ANA test.
Anti-mitochondrial antibodies and Reynolds syndrome	The anti-mitochondrial antibodies (AMA) are considered sensitive and highly specific antibodies. There are nine different subclasses of AMA (M1 to M9). The AMA directed against components M2 (pyruvate dehydrogenase complex), M4 (sulfite oxidase), M8 and M9 (glycogen phosphorylase) are very frequently associated with primary biliary cirrhosis (>95% of patients). Reynolds syndrome is the association of systemic sclerosis (a variant with limited skin involvement) and primary biliary cirrhosis. The main symptoms are itching and fatigue.
Antinuclear antibodies (ANA)	Autoantibodies directed against components present in the nucleus. Indirect immunofluorescence (IIF) is used to detect them in serum. Titers greater than 1/80 are considered significant. For a correct interpretation, it is necessary to report both the titer and the fluorescence pattern (speckled, nucleolar, centromere, homogeneous).
Arthritis	Spontaneous pain and pain on application of pressure on the joint line - affecting the synovial joints - symmetrically distributed - with, but also without, obvious swelling of the joints themselves.
Conjunctivitis	Presents with redness of the white of the eye (sclera), redness that intensifies on the inside of the eyelids (conjunctival sac).Other possible symptoms: intense lacrimation, feeling of sand in the eye, intolerance to light (photophobia), swelling of the eyelids.
Abdominal pain	Can be a sign of visceral involvement or of vascular involvement in rheumatic diseases (CTDs, systemic vasculitis, auto-inflammatory diseases). One of the most frequent causes is inflammation of the parietal peritoneum (peritonitis).Abdominal pain can vary in magnitude and the signs and symptoms can range from diffuse tenderness, to positive Blumberg's sign, through to acute abdomen with ileus.

(*continued from Table 8*)

Cutaneous erythema	Localised or diffuse redness of the skin. Some sites are particularly suggestive of autoimmune disease (e.g. butterfly rash on the cheeks and bridge of the nose).
Raynaud's phenomenon	Sudden, reversible, bilateral and symmetrical change in the colour of the fingers/toes, tip of the nose, tongue, ears - induced by exposure to cold and/or by emotional stress - characterised by a clear demarcation between the affected and unaffected areas - consists of a first phase of pallor (condicio sine qua non, indicative of ischaemia), followed by a phase of peripheral cyanosis (due to reduced circulation of blood in the small vessels) and/or erythema (evidence of reperfusion of the previously ischaemic areas) - associated, in most cases, with paraesthesias in the same areas (NB: Raynaud's phenomenon must be distinguished from acrocyanosis, a condition characterised by cyanotic discolouration of the fingers and toes, which occurs mainly in the winter months and differs from Raynaud's phenomenon in the absence of clear demarcation between the affected and unaffected skin, and in the reduction/disappearance of the cyanotic discolouration on raising of the limb).
Hypocomplementaemia	Reduced levels of circulating complement components, in particular of C3 and C4, reflecting ongoing complement activation and consumption.
Digital ischaemic lesions	- "rate bite" scarring of the fingertips (due to loss of a small amounts of tissue and cicatricial retraction of the skin) or - small infarctions at the same level or - extensive digital ulcers
Leukothrombocytopenia	Leukopenia (<4000/mm^3) or lymphopenia (<1500/mm^3) on two or more occasions. Thrombocytopenia (<100000/mm^3) on two or more occasions.
"Dry eye"	Dry eye (xerophthalmia) is a disorder caused by insufficient production of tears (hypolacrimation). The most common symptoms are: burning eyes, feeling of sand/foreign body in the eye, and difficulty opening the eyelid on wakening. In the most severe cases, there is pain and blurred vision.
Pericarditis	Acute or chronic inflammation of the pericardium whose main presenting symptom is chest pain, usually very intense, exacerbated by breathing, coughing and changes in posture. There may be electrocardiographic changes (ST-segment elevation in two or three peripheral leads and in the precordial leads V2 a V6). Confirmed by echocardiogram. There can also be forms of constrictive pericarditis due to thickening/fibrosis of the pericardial layers. Its most serious complication is cardiac tamponade.
Purpura	Skin lesions that are initially red and subsequently assume a brownish colour, as an expression of cutaneous vasculitis. Not to be confused with thrombocytopenic purpura. Purpura due to vasculitis is usually palpable.
Scleroedema ("puffy fingers")	Increase in the volume of the fingers associated with loss of definition of the shape of the fingers and skin folds, due to - cutaneous imbibition - dermal imbibition
Skin sclerosis	This is a cardinal feature of the disease which manifests itself as: sclerodactyly: thickening and tightening of the skin of the fingers and toes which adheres to the underlying layers scleroderma proximal to the MCP-MTF joints: thickening of the skin, with bilateral and symmetrical non-pitting induration (increased thickness of the skin proximal to the MCP-MTF joints is always associated with sclerodactyly; otherwise, a scleroderma-like syndrome can be suspected).
Telangiectasias	Ectasias of arterioles, venules and capillaries that disappear on application of fingertip pressure. They can have different shapes: - round and evenly distributed (in the so-called mat-like pattern, typical of systemic sclerosis) - punctiform, on the skin of the fingers - spider-shaped
Uveitis	Inflammation of the uvea. Inflammation affecting ocular structures other than the uvea itself (sclera, cornea, retina etc.) is also often classified as "uveitis". It can involve both eyes. Symptoms can develop rapidly and may include: blurred vision, dark spots "floating" in the visual field, eye pain, eye redness, photosensitivity.

Table 9 - The main rheumatic diseases (CTDs). (*To be continued*)

Systemic lupus erythematosus	Signs and symptoms: ✓ Asthenia, general malaise, fever or low-grade fever, anorexia, weight loss ✓ Facial erythema or "butterfly rash" ✓ Raised erythematous plaques on the face, ears, scalp and sometimes trunk ✓ Panniculitis of the buttocks, legs, abdominal wall ✓ Erythematous-scaly papules or plaques, small or developed into ring-like patterns with polycyclic contours, typically in light-exposed areas ✓ Vasculitis ✓ Raynaud's phenomenon ✓ Xerostomia and/or xerophthalmia ✓ Lesions of the oral, nasal and anogenital mucosa ✓ Arthralgias, without signs of inflammation, through to arthritis proper, with pain and functional limitation, symmetrically involving the small joints (hands, wrists) and knees, non-erosive; sparing of the spine ✓ Myalgia, affecting the deltoid and quadriceps in particular; muscle weakness that may be, instead, be a consequence of steroid treatment (steroid myopathy) ✓ Neuropsychiatric symptoms (anxiety or mood disorders, psychosis, cognitive deficits, focal or generalised seizures, recurrent headache, mono- or polyneuropathy, stroke or TIA) ✓ Recurrent serositis (pericarditis, pleurisy) ✓ Pulmonary involvement ✓ Myocarditis, endocarditis ✓ Coronary heart disease ✓ Pulmonary artery hypertension ✓ Peripheral oedema Exclusion of drug-induced SLE: ✓ drugs known and proven to be capable of inducing SLE: hydralazine, procainamide, isoniazid, methyldopa, chlorpromazine and quinidine; ✓ drugs potentially capable of inducing SLE: anticonvulsants, antithyroid drugs, D-penicillamine, sulfasalazine, beta-blockers and thiazide diuretics; ✓ other drugs reported in the literature: minocycline, valproic acid, interferon-α (IFN-α), interleukin-2 (IL-2), clobazam, lamotrigine, TNF-α inhibitors, ACE inhibitors, ticlopidine, amiodarone, lipid-lowering drugs, penicillin, tetracycline, streptomycin, phenylbutazone, oestrogens and oral contraceptives, para-aminosalicylic acid, reserpine Laboratory findings: ✓ ANA positivity ✓ Anti-dsDNA positivity ✓ Anti-ENA positivity (especially for RNP, Sm, SSA/Ro and SSB/La antibodies) ✓ Reduced levels of complement fractions C3 and C4 ✓ prolonged PTT-ratio ✓ Anti-cardiolipin/anti-β2GPI ✓ Anaemia ✓ Leukopenia (<4000/mm3) or lymphopenia (<1500/mm^3) on two or more occasions ✓ Thrombocytopenia (<100000/mm^3) on two or more occasions ✓ Marked increase in ESR, with near normal or normal PCR ✓ Reduced serum creatine, proteinuria > 500 mg/24h, cellular casts in urinary sediment (erythrocytes, granulocytes, tubular cells, mixed) Instrumental parameters (based on symptoms): ✓ Echocardiogram showing left and/or right functional impairment, presence of pericardial effusion ✓ Lung HRCT scan ✓ Brain MRI showing ischaemic damage or vasculitic changes
MCTD	Signs and symptoms: ✓ Raynaud's phenomenon ✓ Bilateral swelling of the hands, with swollen sausage-like fingers ✓ Lupus-like skin rashes, with macules, papules and purpura ✓ Dermatomyositis-like lesions, with Gottron's papules and heliotrope rash ✓ Scleroderma-like skin manifestations ✓ Polyarthritis, possibly evolving into the erosive form ✓ Peritendinous nodules of hands, feet, elbows

(*continued from Table 9*)

	✓ Myositis ✓ Reflux oesophagitis ✓ Pericarditis ✓ Interstitial lung disease ✓ Pulmonary artery hypertension ✓ (mixed symptoms of scleroderma, poly/dermatomyositis, lupus) ✓ Trigeminal neuralgia ✓ Aseptic meningitis Laboratory findings: ✓ ANA positivity ✓ Anti-ENA positivity for antiRNP (U1-RNP) with high titres Instrumental parameters: ✓ Capillaroscopy with scleroderma-like pattern ✓ Esophagogastro-duodenoscopy (*EGD*) showing alteration of the esophagogastric junction ✓ Echocardiogram showing verrucous, mainly mitral, endocarditis; pericardial effusion ✓ PFR test showing abnormal volumes and DLco ✓ Lung HRCT showing interstitial disease
Poly/dermatomyositis	Signs and symptoms: ✓ Fatigue, anorexia, morning stiffness ✓ Symmetrical weakness of proximal muscles ✓ Dysphagia ✓ Dysphonia ✓ Arthromyalgia ✓ Slight crackling (rattling) sound on pulmonary auscultation ✓ Gottron's papules (macular or raised pink-purplish areas on the dorsal surfaces of the interphalangeal joints, elbows, kneecaps and medial malleoli bilaterally) ✓ Heliotrope rash (purplish rash affecting the eyelids) associated with periorbital oedema ✓ Macular erythema of the face, whole neck, posterior surface of the shoulders, upper chest, forearms Laboratory findings: ✓ Significantly increased CK levels ✓ Increased AST, ALT, LDH, aldolase, myoglobin levels ✓ Increased ESR (>50 only in 20% of cases) Instrumental parameters: ✓ Pathognomonic EMG signs ✓ Muscle biopsy Exclusion of: ✓ Disorders of the central and peripheral nervous system including motor neuron disorders with fasciculations, signs of pyramidal involvement, sensory disturbances, reduced nerve conduction velocity, muscle biopsy showing stacked monotypic, atrophic fibres ✓ Muscular dystrophy ✓ Granulomatous myositis (sarcoidosis) ✓ Infections such as trichinosis, schistosomiasis, trypanosomiasis, staphylococcosis, toxoplasmosis ✓ Use of drugs or toxic substances (alcohol, clofibrate, statins), rhabdomyolysis caused by infection, trauma, intense physical exercise, occlusion of the arteries, prolonged coma or convulsions, malignant hyperpyrexia or heat stroke ✓ Metabolic disorders such as McArdle syndrome ✓ Endocrine diseases, focusing particularly on thyroid and adrenal function (hyper-hypothyroidism, Cushing's syndrome, diabetes, hypo-hyperparathyroidism) ✓ Myasthenia gravis

(*continued from Table 9*)

Sjögren syndrome	Signs and symptoms: ✓ Asthenia, fatigue, fever, mild cough ✓ Xerostomia and xerophthalmia ✓ Feeling of "sand in the eyes" ✓ Feeling of reduced salivation, difficulty chewing, frequent need to ingest fluids, intolerance of spicy foods, dysgeusia, chronic burning sensation in the mouth ✓ In women: vaginal dryness with dyspareunia ✓ Swelling of the major salivary glands ("hamster face") ✓ Dry skin, often associated with itching and decreased sweating ✓ Rheumatoid-like arthritis, non-erosive ✓ Peripheral neuropathy, more typically of the lower limbs, with numbness and tingling or burning dysesthesia ✓ Lymphadenopathy ✓ Irritable bladder ✓ Symptoms of hypothyroidism (feeling of cold, ideomotor slowing arterial hypotension, relative bradycardia, worsening constipation) Exclusion of: ✓ Head and neck radiotherapy ✓ HCV infection, AIDS ✓ Pre-existing lymphoma ✓ Sarcoidosis ✓ GVHD ✓ Use of anticholinergic drugs Laboratory findings: ✓ Anti-ENA positivity for SSA/Ro and SSB/La ✓ ANA positivity ✓ FR positivity ✓ Polyclonal hypergammaglobulinaemia ✓ Anti-TPO positivity (in overt thyroid function abnormalities, alterations in the levels of TSH, FT3 and FT4) Instrumental parameters: ✓ Reduced Schirmer's test result (< 5 mm of moisture on the filter paper after 5 minutes of exposure to tears) ✓ Low Tear Beak-Up Test result (tear film breaks up before 10 sec of observation under a slit lamp) ✓ Ultrasound of the salivary glands with parenchymal abnormalities and/or the presence of intraparenchymal lymphopathy ✓ Salivary gland scintigraphy showing reduced function ✓ Focal infiltrates of mononuclear cells in salivary gland biopsy specimen
UCT	Signs and symptoms lasting longer than a minimum of 3 years: ✓ Asthenia, general malaise, fever ✓ Arthritis and arthralgia ✓ Raynaud's phenomenon ✓ Pleuro-pericarditis ✓ Xerophthalmia and other symptoms typical of Sjögren syndrome ✓ Skin manifestations (photosensitivity, rash) ✓ Manifestations of central nervous system involvement ✓ Peripheral neuropathy ✓ Vasculitis ✓ Myositis Exclusion of: ✓ Defined CTD Laboratory findings: ✓ ANA positivity with a titre higher than 1/320 in two samples analysed at a distance of at least 6 months Instrumental parameters: ✓ None Classification/diagnostic criteria: - Signs and symptoms of CTD that cannot be better classified - ANA positivity with a thigh titre on at least two occasions - Clinical symptoms must have been present for at least 3 years

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