



Connective Tissue Diseases and the Internist - Classification, Nomenclature or Just Semantics

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ABSTRACT

Being multisystem illnesses, connective tissue diseases (CTDs) frequently enter the domain of internists. The terms CTD, undifferentiated connective tissue disease (UCTD) and mixed connective tissue disease (MCTD) are often used incorrectly. Most clinicians are confused by classification criteria, of which there is an abundance in rheumatology! Criteria are meant to supplement and not replace good clinical judgement, which retains its primacy in day to day practice. This chapter simplifies the concept of CTDs and explains the principle behind, and limitation of, criteria used to classify rheumatic diseases.

INTRODUCTION

The concept of connective tissue diseases (CTDs) owes much to the seminal work of Klemperer and colleagues. In the early part of 20th century physicians dealing with systemic lupus erythematosus (SLE) were hard put to explain the myriad disease manifestations on the basis of organ involvement alone. Klemperer, Pollack and Baehr were the first to propose that the morbid process in SLE affects the entire collagenous tissue system where 'fibrinoid degeneration' is the most striking alteration noticed.¹ This resulted in these diseases being referred to as the 'diffuse collagen diseases'. With expanding knowledge of the structure of connective tissue, it soon became clear that collagen was just one component of connective tissue. This led to the replacement of the earlier term 'collagenosis' by 'connective tissue disease', which persists to this day.^{2,3}

The various CTDs include SLE, systemic sclerosis (SSc), Sjogren's syndrome, polymyositis and dermatomyositis and systemic vasculitides. These diseases are characterized by multisystem involvement, persistent inflammation and presence of autoantibodies. The clinical features are diverse and, yet, there is unity among diversity signifying that the concept of CTD remains valid more than 60 years after it was initially proposed. Clinical features common to CTDs include arthritis, rash, Raynaud's phenomenon, serositis, myocarditis etc. The ethos behind this term was to focus on the common clinical features of these diverse illnesses. The idea was not to evoke a single nosological entity having several different manifestations e.g. SLE, scleroderma etc. Klemperer with remarkable prescience felt that the term was liable to be misused as a waste paper basket

term for 'maladies with puzzling clinical and anatomic features'. Unfortunately, many clinicians find the nosologic conundrum baffling and use the term CTD loosely. This chapter briefly explains the nomenclature and classification of CTDs and its relevance to the clinician.

NOMENCLATURE (CTD, UCTD OR MCTD)

The CTDs may present with signs and symptoms that allow categorization into a defined disease entity like SLE or SSc or Sjogren's syndrome. However, on several occasions the clinical features may suggest a CTD but defy categorization into any one defined entity. The term undifferentiated connective tissue disease (UCTD) is used in such a situation. The UCTDs, over a period of time, may evolve into a defined syndrome or stay undifferentiated or disappear (Fig. 1). Nearly 25% of patients with systemic rheumatic diseases exhibit features of two or more diseases, when the term overlap syndrome is used. The overlap may consist of full expression of the features of two or more conditions, or more commonly may be limited to one or more manifestations of each disease.⁴ Mixed connective disease (MCTD) is a term employed for a subset of overlap syndrome that is characterized by the presence of antibodies against ribonucleoproteins (u1 sn RNP). The defining feature of MCTD is these antibodies and it needs to be emphasized that MCTD is a label given only when serology demonstrates antibodies against u1 sn RNP. MCTD is a disease that can be suspected clinically but has to be confirmed serologically. It stands to reason that all patients with MCTD can be included under the broad label of overlap syndrome but not all patients with overlap syndrome have MCTD (Fig. 2).

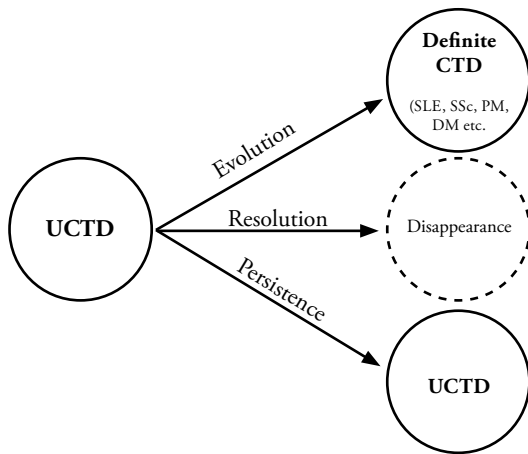


Fig. 1 : Outcome of undifferentiated connective tissue diseases (UCTD)

CTD= Connective tissue disease
 SLE= Systemic lupus erythematosus
 SSc= Systemic sclerosis
 PM= Polymyositis
 DM= Dermatomyositis

CRITERIA AND CLASSIFICATION OF CTDS

Criteria are an unavoidable necessity in this era of evidence-based medicine and are of several different types: classification criteria, prognostic criteria, status indices (activity and chronicity indices), outcome measures and diagnostic criteria.^{5,6} To add to the complexity, criteria do constantly evolve as knowledge advances. For example, SLE criteria were first proposed in 1971, revised in 1982 and further revised in 1997.⁷⁻⁹ To the uninitiated the plethora of criteria used in rheumatology literature⁷⁻²¹ can be quite daunting. In this write up I shall confine myself to classification and diagnostic criteria and their relevance for a clinician. Germane to this discussion is the need to understand that classification criteria evolved in response to the fact that most CTDs lack a single pathognomonic or distinguishing feature. Features like arthritis, fever, Raynaud's phenomenon, skin rash are common to several diseases. Also, many of the features that define an autoimmune rheumatic disease do not occur concurrently but sequentially. These features present in a particular combination along with certain laboratory investigations help identify a specific disease. Classification criteria help differentiate patients with a particular disease from patients with a potentially confusable condition as well as from the normal population (case definition). For example, criteria for SLE would help differentiate lupus from another inflammatory polyarthritis like RA. The issue that classification criteria tend to answer is not whether the patient has a disease, but which disease does the patient have.⁵ Classification criteria serve several useful purposes: provide uniformity for patients being included in epidemiological studies and trials, facilitate comparison between different centers and provide a lingua franca for scientific communication. However, at the bedside the role of classification criteria is rather limited. The clinician would do well to remember that classification criteria, despite being (mis)used as surrogate diagnostic criteria, are not meant (and were never meant) to be used for diagnostic purposes. This difference is crucial.

Key Points about Connective Tissue Diseases (CTDs)

- Connective tissue diseases share several common clinical features
- Categorisation into a definite entity is not always possible
- Delineation of organ involvement is more important than diagnostic labels
- Organ involvement determines treatment decisions
- Classification criteria are important for research and epidemiologic purposes
- The utility of classification criteria in routine clinical practice is limited
- Classification criteria are not the same as diagnostic criteria
- The diagnosis in a given individual should not be based merely on the presence or absence of classification criteria
- Classification criteria are 'adjuncts to' and not 'substitutes for' rational evidence-based clinical judgment

'Classification' criteria are applied to groups and are more specific than 'diagnostic' criteria which are applied to individuals and are more sensitive. The clinician dealing with an individual patient need not be fettered by classification criteria which are important but not indispensable. It is worthwhile to note that most criteria available are 'classification' criteria and not 'diagnostic' criteria. In general, diagnostic criteria for CTDs do not exist. This is because there is no 'gold standard' for making a diagnosis. Making a diagnosis is a complex process which integrates history, physical examination and laboratory investigations into evidence-based clinical decision-making. Diagnosis making and treatment decisions cannot be constrained by lack of classification criteria, especially since several individuals with a CTD may not initially or ever meet the classification criteria. To elaborate, a young woman with malar rash and a positive antinuclear antibody would merit a diagnosis of SLE but would not be classified as SLE for purposes of a clinical study. The fact that an individual does not meet the classification criteria for a particular CTD does not exclude that diagnosis at the bedside.

Classification criteria, if their sensitivity and specificity were to be 100%, could indeed serve as diagnostic criteria! Alas, this is never the case in actual clinical practice. When applied to a population setting, the positive predictive value of classification criteria is decreased and a fairly large number of people may be misclassified as false positives.⁵

IMPLICATIONS FOR A CLINICIAN

From the foregoing discussion it is clear that classification criteria serve a rather limited role in clinical decision-making and diagnosis at the bedside. The clinician should aim to delineate the organ involvement in every patient with CTD. This involves a thorough physical examination and judicious use of investigations. Urinalysis is a very important but underutilized investigation. All patients with CTD require periodic urinalysis to detect proteinuria, hematuria and casturia suggestive of renal involvement which is usually asymptomatic but has a major bearing on prognosis. Therapy is directed according to organ involvement. For example, the arthritis of CTD, whether SLE or SSc, would be treated with hydroxychloroquine, methotrexate or sulfasalazine in addition to NSAIDs. Similarly, myocarditis and

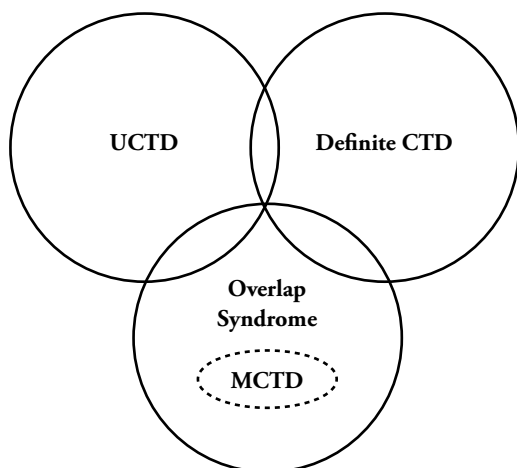


Fig. 2: Spectrum of connective tissue diseases (CTD).

UCTD – Undifferentiated connective tissue disease

MCTD – Mixed connective tissue disease

nephritis would warrant corticosteroids with or without additional immunosuppressives like azathioprine and cyclophosphamide. Treatment decisions should never be postponed or delayed pending classification.

CONCLUSIONS

The delineation of extent of organ involvement in CTDs is far more important than labels. Clinicians should refrain from floundering in semantic depths. Classification criteria, while important in a research setting and for epidemiologic purposes, play a limited role in bedside decision-making in a given patient. Criteria are meant to assist and not hamper clinical decision-making. Therapeutic decisions in an individual patient should not be governed solely by fulfillment or lack of fulfillment of criteria. The dictum in clinical rheumatology is ‘treat the patient and do not chase the classification criteria’.

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