Undifferentiated connective tissue diseases (UCTD)

M. Mosca *, C. Tani, C. Neri, C. Baldini, S. Bombardieri

Rheumatology Unit, Department of Internal Medicine, University of Pisa, Via Roma, 67, 56126 Pisa, Italy

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Abstract

The term undifferentiated connective tissue diseases is used to define conditions characterized by the presence of signs and symptoms suggestive of a systemic autoimmune disease that do not satisfy the classificative criteria for defined connective tissue diseases (CTD) such as systemic lupus erythematosus (SLE), Sjögren’s syndrome (SS), rheumatoid arthritis (RA) and others.

A small percentage of patients presenting with an undifferentiated profile will develop during the first year follow up of a full blown CTD, however an average of 75% will maintain an undifferentiated clinical course. These patients may be defined as having a stable undifferentiated connective tissue diseases (UCTD).

The most characteristic symptoms of UCTD are represented by arthritis and arthralgias, Raynaud’s phenomenon, leukopenia, while neurological and kidney involvement are virtually absent. Eighty percent of these patients have a single autoantibody specificity, more frequently anti-Ro and anti-RNP antibodies.

Stable UCTD are considered as distinct clinical entities and therefore it has been proposed to define those conditions as UCTD. Classificative criteria have also been proposed and a work to better define them is still under way.

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1. Undifferentiated connective tissue diseases

The clinical onset of connective tissue diseases may be undifferentiated and its common clinical experience is the existence of conditions characterized by the presence of clinical and serological manifestations suggestive of autoimmune diseases but not sufficient to make a diagnosis of a defined CTD [1–9], these conditions have

* Corresponding author.

been variably defined as incomplete systemic lupus erythematosus, latent lupus, early undifferentiated connective tissue diseases, undifferentiated connective tissue diseases [10–30].

The main clinical manifestations at onset of these undefined diseases are represented by arthralgias (66%), arthritis (32%), Raynaud’s phenomenon (38%), leukopenia (24%), xerostomia and xerophthalmia (21%), thrombocytopenia (9%), serositis (4%), photosensitive rash (3%). It may be difficult to distinguish these conditions
from early phases of defined diseases such as systemic lupus erythematosus (SLE), Sjögren’s syndrome (SS), rheumatoid arthritis (RA), systemic sclerosis (SSc) and many others. It is well known, in fact, that the onset of many defined CTDs may not be characterized by disease specific manifestations, such as for example glomerulonephritis in SLE.

Therefore, in the assessment of patients presenting with an undifferentiated onset, it would be important to be able to understand whether this is the onset of a defined disease or rather a condition that will remain undefined over time [10]. From the existing literature it is evident that an average of 25% of patients with an undifferentiated disease at onset will evolve to defined CTDs during the follow up; the evolution occurring early in the disease and generally within the first 5 years of follow up [11,12,15–25,27–30].

As reported in Table 1, undifferentiated diseases may evolve to various defined CTDs, although the evolution to SLE seems to occur more frequently [11,12,15–25,27–30]. Predictive factors for the evolution to defined CTDs have been identified (Table 2) [15,17,19–25,27–30]. In particular the presence of anti-dsDNA antibodies, of anti-Sm antibodies, anti-phospholipid antibodies or the presence of multiple antibodies specificities and among clinical manifestations, serositis, alopecia, photosensitivity and discoid rash, were predictive for an evolution to SLE in many studies [15,19–21,27–30].

Less data are available concerning predictive factors for the evolution to other CTDs. Raynaud’s phenomenon, xerostomia, anti-Ro and anti-La antibodies were correlated with an evolution to SS [28,30]. Raynaud’s phenomenon, sclerodactyly, esophageal dysfunction, positive ANA with nucleolar pattern were correlated with an evolution to SSc [21,30]. Polyarthritis, positive rheumatoid factors, and an increased ESR were correlated with a possible evolution to RA [30].

It is important to note, however, that these latter associations, derive from single studies and probably reflect the different assessment that patients undergo at the time of diagnosis and therefore need to be interpreted cautiously.

No triggering factors for the evolution of undifferentiated diseases to defined CTDs have been so far identified, therefore it appears important to strictly monitor patients particularly at disease onset and also in particular conditions, such as for example pregnancy, which are known to interfere with the clinical course of systemic autoimmune diseases [29].

### 2. Clinical and serological manifestations

From the data reported it appears that a small percentage of patients with an undifferentiated onset, will evolve to defined CTDs while the majority of them will remain undifferentiated during the course of the disease. Many authors have used the term undifferentiated connective tissue diseases (UCTD), to identify stable undifferentiated diseases. In the next part of this paper we will therefore use the definition UCTD to refer to stable undifferentiated conditions.

There are no specific signs or symptoms of UCTD, in fact as previously reported, these diseases present clinical manifestations common to other CTDs. The most frequent clinical manifestations of UCTD are arthralgias (37–80%), arthritis (14–70%), Raynaud’s phenomenon (45–60%), leukopenia (11–42%), anemia, xerostomia (7–40%), xerophthalmia (8–36%). Other clinical manifestations are reported in Fig. 1 [11–14,16,17,21,24,25,27–31].

It is clear that the clinical profile of UCTD is characterized by the absence of major organ involvement, particularly kidney and central nervous system and is generally mild. During the follow up the symptoms improve and mild disease flares are seen occasionally.

About 90% of the UCTD patients have positive ANA; anti-Ro antibodies are present in 8–30% of the patients and anti-RNP in 10–30%. Less frequently positive anti-dsDNA anti-phospholipid antibodies are observed [14,17,19,21,22,26–29]. Interestingly, 80% of these patients have a simple autoantibody profile characterized by a single antibody specificity, usually anti-Ro or anti-RNP antibodies [17,28,29].

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### Table 1

Evolution of undifferentiated diseases to defined connective tissue diseases (CTD)

<table>
<thead>
<tr>
<th>Defined CTD</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE</td>
<td>[11,12,17,27]</td>
</tr>
<tr>
<td>SLE+other CTD:</td>
<td>[15,19–21,23,28,30]</td>
</tr>
<tr>
<td>• LES</td>
<td>8–21%</td>
</tr>
<tr>
<td>• SS</td>
<td>2–18%</td>
</tr>
<tr>
<td>• SS</td>
<td>4–15%</td>
</tr>
<tr>
<td>• MCTD</td>
<td>0.5–3%</td>
</tr>
<tr>
<td>• PM</td>
<td>0.6–2%</td>
</tr>
<tr>
<td>• AR</td>
<td>3–26%</td>
</tr>
</tbody>
</table>

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### Table 2

Predictive factors for the evolution to defined connective tissue diseases (CTD)

<table>
<thead>
<tr>
<th>Predictive variables identified</th>
<th>[15,21,30]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No predictive variables</td>
<td>[11,17]</td>
</tr>
</tbody>
</table>

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- Clinical variables
- Serological variables

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The autoantibody profile remains stable over time and new autoantibody specificities are rare and usually observed in those patients who will evolve to defined CTDs [17].

As these are mild and benign conditions, only a small percentage of UCTD are treated. The most widely used drugs are NSAID (40%), low dose corticosteroids (30–50%) and antimalarials (10–30%) [12,17,27].

3. Classificative criteria

Classificative criteria generally accepted and validated, able to identify UCTD patients are not yet available. On the basis of the existing literature, however, preliminary classificative criteria have been proposed to distinguish between early and stable undifferentiated diseases.

On the basis of these criteria UCTD are those conditions characterized by (i) signs and symptoms suggestive of a connective tissue disease, but not fulfilling the criteria for any defined CTDs, (ii) positive antinuclear antibodies, and (ii) a disease duration of at least 3 years. Patients with a shorter follow up should be defined having as early UCTD and include patients who will develop a defined CTD and those with transitory manifestations [23].

4. Conclusions

Undifferentiated connective tissue diseases are systemic autoimmune conditions characterized by a mild clinical profile and a simplified autoimmune repertoire. Although these conditions are generally benign, an evolution to CTDs is reported and changes in the disease course may occur. Therefore a regular follow up of these patients is advised particularly in the first year of the disease. A strict monitoring is also advised in conditions which may interfere with the course of autoimmune diseases such as for example pregnancy.

References

Anti-Jo-1 antibody positive polymyositis – successful therapy with leflunomide

Idiopathic inflammatory myopathies (IM), including dermatomyositis (DM) and polymyositis (PM), are a group of systemic rheumatologic diseases of unknown etiology characterized by chronic myositis. Antisyntetase antibodies such as the anti-Jo-1 antibody are known to be highly specific for inflammatory myopathies. Patients with this antibody frequently show a combination of symptoms including interstitial lung disease, fever, polyarthritis, myositis, Raynaud's phenomenon and "mechanic's hands". In the management of PM with anti-Jo-1 antibody, immunosuppressive agents are used to control the disease. Leflunomide is a new immunosuppressive drug recently introduced in the treatment of female patients with PM and anti-Jo-1 antibodies. In this study, Lange U. et al. (Autoimmunity 2006; 39: 261-4) report two cases of female patients with PM and anti-Jo-1 antibodies, who were successfully treated with leflunomide.