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REVIEW ARTICLE

Immune-Mediated Multi-Organ Syndromes: Diagnostic Challenges and the Role of Artificial Intelligence

Syndromes d'atteinte multi-systémique dysimmunitaire : défis diagnostiques et rôle de l'intelligence artificielle

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MOTS CLÉS

Intelligence artificielle ;
Maladies auto-immunes ;
Algorithmes diagnostiques ;
Syndromes de chevauchement

Résumé

Les syndromes multi-organes d'origine immunitaire, en particulier la connectivite mixte et le syndrome des anti-synthétases, posent un véritable défi diagnostique en médecine interne du fait de leurs manifestations cliniques chevauchantes et souvent atypiques. En brouillant les frontières entre différentes maladies auto-immunes systémiques, ces syndromes entraînent des retards diagnostiques et une incertitude thérapeutique. Dans ce contexte, l'intelligence artificielle apparaît comme un outil prometteur, capable grâce à l'apprentissage automatique d'intégrer des données cliniques et biologiques complexes. Cette revue analyse les difficultés diagnostiques majeures de ces syndromes, met en lumière les limites des classifications actuelles et propose un arbre décisionnel enrichi par l'IA pour améliorer la précision du diagnostic et la précocité de la prise en charge.

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KEYWORDS

Artificial Intelligence ;
Autoimmune Diseases ;
Diagnostic Algorithms ;
Overlap Syndromes

Abstract

Immune-mediated multi-organ syndromes, notably mixed connective tissue disease and anti-synthetase syndrome, challenge internists due to their overlapping and atypical features. These conditions blur the lines between systemic autoimmune diseases, delaying diagnosis and complicating treatment. In this context, artificial intelligence emerges as a valuable ally, using machine learning to integrate complex clinical and biological data. This review discusses the diagnostic complexity of these syndromes, critiques current classification systems, and proposes an AI-assisted decision tree to improve diagnostic accuracy and therapeutic timing.

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Introduction

Systemic autoimmune diseases (SADs) such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), and Sjögren's syndrome (SS) often present with overlapping and heterogeneous clinical manifestations [1]. Patients may exhibit signs of more than one autoimmune disorder simultaneously, resulting in the classification of overlap syndromes. Examples include mixed connective tissue disease (MCTD), defined by anti-U1 RNP antibodies, and the anti-synthetase syndrome (ASS), characterized by anti-aminoacyl-tRNA synthetase antibodies such as anti-Jo-1, along with myositis, arthritis, and interstitial lung disease [2,3]. These disorders challenge internists due to their protean presentations and overlapping immunological profiles.

The diagnostic process is further complicated by the absence of universally accepted criteria, the variability in disease evolution, and the frequent occurrence of incomplete or atypical syndromes [4]. While specific autoantibodies provide valuable clues, they are not always definitive or sufficiently sensitive to distinguish between entities. As a result, misclassification and diagnostic delays remain common in clinical practice [5].

In response to these challenges, artificial intelligence (AI) has emerged as a promising tool to enhance diagnostic accuracy. Machine learning algorithms can analyze complex clinical and laboratory data, identify hidden patterns, and propose probabilistic diagnoses, particularly in diseases with overlapping features [6]. Recent applications in rheumatology have demonstrated that AI can support early detection, risk stratification, and treatment planning for autoimmune diseases [7].

This article provides a pedagogical overview of immune-mediated multi-organ syndromes, emphasizing diagnostic strategies in internal medicine and exploring how AI-driven tools can contribute to more accurate and timely clinical decision-making.

Methods

This narrative review was designed to synthesize current knowledge on immune-mediated multi-organ syndromes, particularly focusing on their diagnosis and the potential contribution of artificial intelligence (AI). An extensive search of the PubMed, Scopus, and Web of Science databases was performed, covering the period from January 2015 to April 2025.

The following search terms and combinations were used: "autoimmune overlap syndromes", "connective tissue diseases", "anti-synthetase syndrome", "mixed connective tissue disease", "systemic autoimmunity", "diagnostic delay",

"artificial intelligence in rheumatology", "clinical decision support systems", "machine learning", and "internal medicine". Only articles published in English and involving human subjects were considered. The inclusion criteria comprised original research articles, systematic reviews, expert consensus documents, and case series relevant to the diagnosis and classification of systemic autoimmune diseases and their overlap syndromes.

Special attention was given to publications exploring the integration of AI tools in the diagnostic process. Studies addressing algorithms for differential diagnosis, risk prediction models, AI-assisted image interpretation (e.g., HRCT, MRI), and serological profiling using machine learning techniques were included. Articles without sufficient methodological detail or relevance to internal medicine practice were excluded.

In addition to database queries, manual screening of reference lists from included studies was performed to identify potentially relevant literature not captured in the initial search. The information gathered was categorized thematically into four domains: (1) clinical and immunological characteristics of overlap syndromes; (2) diagnostic limitations in internal medicine; (3) AI applications in autoimmune disease diagnostics; and (4) conceptual models integrating AI-assisted decision-making.

Additionally, reference lists of selected publications were screened to identify further relevant sources. Information was synthesized thematically, focusing on diagnostic challenges, the clinical utility of specific autoantibodies, and the integration of AI models in medical diagnostics.

Results

1. Clinical and immunological spectrum of overlap syndromes :

Overlap syndromes represent a diagnostically challenging subgroup of systemic autoimmune diseases, characterized by features shared across multiple well-defined connective tissue disorders. Mixed connective tissue disease (MCTD), for example, involves overlapping features of SLE, SSc, and PM, along with high titers of anti-U1 RNP antibodies [8]. The anti-synthetase syndrome (ASS), on the other hand, is hallmarked by the presence of aminoacyl-tRNA synthetase antibodies (particularly anti-Jo-1) and commonly presents with myositis, interstitial lung disease (ILD), non-erosive arthritis, Raynaud's phenomenon, and mechanic's hands [9,10].

Clinically, these syndromes often exhibit progressive, multi-organ involvement and systemic inflammation, with common presentations including respiratory symptoms,

arthralgia, myalgia, fatigue, and cutaneous manifestations [11]. Internists must recognize atypical and incomplete presentations, as patients may not fulfill the full criteria for any single entity. Immunologically, autoantibody profiling remains a cornerstone of diagnosis. Anti-RNP, anti-Jo-1, anti-Mi-2, and anti-PL-7/PL-12 are particularly relevant in classifying these overlaps [12,13]. However, antibody specificity and clinical correlations are not absolute, adding to diagnostic ambiguity [14].

2. Diagnostic challenges :

Diagnosing systemic autoimmune diseases with overlapping features remains a formidable task, especially in early stages where clinical findings are nonspecific. Diagnostic criteria for SLE (EULAR/ACR 2019), systemic sclerosis (ACR/EULAR 2013), and idiopathic inflammatory myopathies (EULAR/ACR 2017) are primarily designed for classification rather than early diagnosis, and often fail to capture overlap syndromes [15,16].

Clinical reasoning is further hampered by variability in disease onset, multi-systemic involvement, and evolving serologies. The presence of only one or two defining features at presentation may lead to underdiagnosis or misclassification [17]. Furthermore, the interpretation of ANA patterns, ENA panels, and HRCT imaging often requires expert consensus, and even experienced clinicians may encounter delays in reaching a definitive diagnosis [18].

The use of algorithms or scoring systems such as the Kahn criteria or the CREST variant in systemic sclerosis can be informative, but remain insufficient in overlap settings. Delays in diagnosis can exceed 12 months in many patients, particularly in low-resource settings or where access to immunological testing is limited [19].

3. Artificial intelligence in autoimmune disease diagnosis :

AI-based tools, particularly those employing machine learning (ML), have gained traction in recent years as aids for diagnostic decision-making in complex diseases such as SADs. Models using supervised learning algorithms—including random forests, decision trees, and neural networks—have been trained on structured clinical and serological data to differentiate autoimmune diseases with high accuracy [20,21]. CNNs have shown promise in interpreting HRCT scans to distinguish ILD subtypes in ASS patients [22], while other systems have been used to analyze ANA patterns and antibody profiles with greater consistency than human evaluators [23]. A study by Wang et al. (2023) demonstrated that ML models could outperform rheumatologists in classifying early-onset undifferentiated connective tissue disease [24].

Importantly, AI does not replace clinical judgment but augments it by identifying patterns not easily discernible by humans. Integration of electronic health records, real-time laboratory data, and imaging into AI systems is currently under evaluation in several centers, with encouraging preliminary results [25].

4. A Conceptual AI-Supported Diagnostic Tree :

We present a conceptual diagnostic decision tree that incorporates AI logic into clinical reasoning. The proposed framework ingests data such as clinical features (arthralgia, myositis, ILD), laboratory values (autoantibodies, ESR, CRP), and imaging (HRCT findings, musculoskeletal MRI) to produce a ranked list of probable diagnoses. Each branch of the decision tree is modulated by the probabilistic influence of key variables, refined through AI training datasets.

For instance, the presence of symmetric arthritis, positive anti-RNP, and skin involvement would activate branches toward MCTD, whereas anti-Jo-1 positivity and ILD would reroute toward ASS. The AI module recalibrates the weighting as new data become available (e.g., follow-up labs), allowing for a dynamic diagnostic process.

Such models can be embedded into clinical decision support systems (CDSS) used in hospital information systems. While still largely experimental, early validation studies report increased diagnostic efficiency, reduced inter-observer variability, and improved early detection of complex cases [26,27].

Discussion

Systemic autoimmune overlap syndromes pose persistent challenges in internal medicine due to their variable clinical presentations, evolving serological profiles, and often inconclusive classification frameworks. These syndromes, such as MCTD and ASS, do not always fit within the strict boundaries of existing diagnostic criteria, especially in early or incomplete forms of the disease [28]. The delayed diagnosis in many cases—often extending beyond a year—can lead to suboptimal treatment outcomes, increased organ damage, and diminished quality of life [29,30].

Autoantibody profiling remains central to the diagnosis, yet variability in antibody expression and overlap between specificities (e.g., anti-RNP in both MCTD and SLE) contributes to diagnostic ambiguity. Furthermore, clinical signs such as Raynaud's phenomenon, arthritis, or ILD are not specific and may appear in numerous autoimmune conditions [31]. As such, internists must adopt a comprehensive syndromic approach, integrating clinical, serological, and imaging data over time.

In this landscape, artificial intelligence (AI) offers transformative potential. AI systems can synthesize multidimensional data—ranging from

structured lab results to radiological images and clinical narratives—to detect latent patterns, suggest probabilistic diagnoses, and guide clinicians through complex decision trees [32]. Notably, studies have demonstrated that ML algorithms outperform traditional statistical models in distinguishing between overlapping autoimmune diseases and can predict disease progression with increasing accuracy [33,34].

One promising approach involves the construction of decision-support algorithms using supervised learning. These algorithms are trained on annotated datasets comprising thousands of patient records, each labeled with diagnostic outcomes and linked to relevant clinical features. The algorithm learns associations between variables such as autoantibody panels, clinical symptoms (e.g., arthritis, ILD, rash), and imaging findings (e.g., HRCT features of fibrosis), ultimately generating a probability score for differential diagnoses like MCTD, ASS, or undifferentiated connective tissue disease [35].

Advanced models may incorporate ensemble methods (e.g., random forests or gradient boosting) to improve performance and reduce overfitting. Others employ neural networks capable of processing unstructured data such as free-text clinical notes or radiological images [36]. The resulting system can dynamically update diagnostic probabilities as new data points become available—mimicking the iterative reasoning process of experienced clinicians. Importantly, these tools can be implemented in clinical dashboards, offering ranked differential diagnoses alongside recommendations for confirmatory testing.

Despite these advances, several barriers hinder the widespread adoption of AI in clinical practice. These include the need for high-quality, annotated datasets for training, concerns over data privacy and algorithmic bias, and the lack of standardized validation protocols across different healthcare settings [37,38]. Furthermore, there remains skepticism among clinicians regarding the interpretability and transparency of AI-generated outputs—known as the "black box" problem [39].

To ensure clinical relevance, AI tools should be developed collaboratively with clinicians and designed to be interpretable, auditable, and seamlessly integrable into electronic health records. Hybrid models that combine rule-based logic (e.g., existing classification criteria) with machine learning predictions may provide an optimal balance of explainability and performance [40].

In conclusion, the integration of AI into the diagnostic process of immune-mediated multi-organ syndromes holds great promise. By enhancing diagnostic precision, reducing variability, and assisting with early identification,

AI can empower internists to manage these complex diseases more effectively. However, future efforts must focus on rigorous clinical validation, interdisciplinary collaboration, and ethical deployment to fully realize this potential.

Conclusion

Immune-mediated multi-organ syndromes, such as MCTD and anti-synthetase syndrome, represent a major diagnostic challenge in internal medicine due to their overlapping features and evolving immunologic profiles. Current classification systems are often insufficient, leading to delayed diagnosis and suboptimal care. Artificial intelligence, particularly through machine learning, emerges as a valuable asset capable of analyzing complex datasets to support early and accurate diagnosis. AI-based decision tools could enhance clinical reasoning, but their implementation must be transparent, ethically sound, and clinically integrated. Future progress depends on interdisciplinary collaboration to develop reliable, validated AI systems that can support more personalized and proactive care.

Conflict of Interest Statement

The authors declare no conflicts of interest in connection with this work.

Acknowledgements

The authors would like to thank all members of the Department of Internal Medicine at CHU Beni Messous, as well as the hospital's scientific council, the DAMP, and the general administration for their support.

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