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Association of Rheumatoid Arthritis and Amyotrophic Lateral Sclerosis: Shared Genetic and Pathophysiologic Mechanisms

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Abstract

Rheumatoid arthritis and amyotrophic lateral sclerosis are two distinct diseases affecting millions and thousands respectively each year. Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder primarily affecting synovial joints, while amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting motor neurons. Although these conditions have traditionally been considered distinct, emerging evidence suggests potential immunogenetic and pathophysiologic overlaps. Studies exploring an association between Rheumatoid arthritis and amyotrophic lateral sclerosis (ALS) in modern or previous literature have been limited.

Several cases have highlighted a potential link between the two diseases [1]. Comparison and identification of concurrence and correlation can prove challenging due to overlapping in symptoms such as joint pain and fatigue in RA masking muscle weakness in ALS. We present a case-based review with a case of a 71-year-old female patient with long-standing RA who presented with fatigue, slurred speech and difficulty walking and was subsequently diagnosed with slowly progressing primary lateral sclerosis (PLS) form of adult-onset hereditary cerebellar degeneration (AHCD). Only other five cases of this rare association have been previously described in literature up until 2011 [2].

Potential shared immunogenetic and pathophysiologic mechanisms of RA and ALS/PLS, such as immune dysregulation, genetic predispositions, inflammatory pathways and finally the potential role of autoimmunity in neurodegeneration are discussed and we show a possible link between these two diseases. Understanding the interactions between these diseases may provide novel insights into the interplay between autoimmunity and neurodegeneration – positively contributing to the need for further research and greater understanding of the disease pathophysiology, potential targeted therapy strategies leading to eventual better patient outcomes.

Keywords: Rheumatoid arthritis (RA), Amyotrophic lateral sclerosis, TNFα, primary lateral sclerosis, anterior horn cell disease; Neuroinflammation; Etanercept, rituximab, tocilizumab, Upadacitinib and stem cell therapy

Abbreviations: RA: Rheumatoid Arthritis; ALS: Amyotrophic Lateral Sclerosis; Pls: Primary Lateral Sclerosis; Ahcd: Adult-Onset Hereditary Cerebellar Degeneration; Cns: Central Nervous System; Dmards: Disease-Modifying Antirheumatic Drugs; Mesh: Medical Subject Headings; Acps: Anti-Citrullinated Protein Antibodies

Introduction

Rheumatoid arthritis (RA) is an autoimmune rheumatic disease characterized by inflammation and destruction of synovial joints, though it can also manifest systemically through inflammatory pathways. Extra-articular involvement, such as scleritis or central nervous system (CNS) complications, is well-documented. It is widely accepted that inflammation at the blood-brain barrier facilitates the transfer of autoantibodies from the blood to the cerebrospinal fluid, contributing to CNS involvement in rheumatic diseases. The mechanisms underlying RA have been extensively studied, leading to a range of treatments, from disease-modifying antirheumatic drugs (DMARDs) like methotrexate to advanced biologic therapies such as etanercept [3].

In contrast, amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder marked by the inflammation and destruction of motor neurons, leading to muscle weakness, paralysis, and eventual respiratory failure [4]. While RA and ALS

have traditionally been viewed as distinct entities, emerging evidence suggests potential overlaps in their immunogenetic and pathophysiologic mechanisms. For instance, shared pathways involving immune dysregulation, genetic predispositions, systemic inflammation and neuroinflammation as explored raise the possibility of a connection between these conditions [5,6].

This case-based review explores a unique presentation of a 71-year-old female with long-standing RA who subsequently developed primary lateral sclerosis (PLS), a variant of ALS. This rare co-occurrence highlights the diagnostic and therapeutic challenges posed by overlapping autoimmune and neurodegenerative conditions. By studying existing literature and analyzing this distinctive case, we aim to investigate potential shared mechanisms, such as the role of autoimmunity in neurodegeneration, and provide novel insights into the interplay between RA and ALS. We also aim to discuss causal factors such as biologic treatment on development of neurodegeneration. The objective of this review is to contribute to further research and a deeper understanding of these diseases, ultimately informing improved diagnostic and therapeutic management strategies.

Case Presentation

A 71-year-old woman with a 35-year history of RA presented to the rheumatology clinic with 5 years of progressive neurological deterioration in the form slurred speech and difficulty walking. The patient's RA had initially been treated with methotrexate. Etanercept was subsequently added which was later switched to rituximab due to inefficacy. She did not respond well to this and was trialled on tocilizumab. She did not respond to this either and was switched to Upadacitinib until 2023. Due to continued disease activity in 2023, she had stem cell therapy in the Cayman Islands after which her RA symptoms went into remission.

Five years ago, she began to develop slurred speech with progressive gait difficulties and undertook an MRI head and EEG which were both reported as normal. Neurophysiological studies reported axonal changes in the lower limbs with moderate partial denervation, mild acute denervation in some lower limb muscles, and fasciculations. Surface EMG detected fasciculations in the rectus abdominis and myokymic potentials in the brachioradialis. She was subsequently diagnosed with slow progressing primary lateral sclerosis (PLS) form of anterior horn cell disease (AHCD. Additional blood tests were conducted to assess inflammatory, autoantibody, biochemical, and endocrine profiles, with results pending review.

Comprehensive Search Strategy

A comprehensive search strategy was employed to assess between rheumatoid arthritis (RA) and amyotrophic lateral sclerosis (ALS). The following databases were searched: PubMed, British Medical Journal, ScienceDirect, and Google Scholar. The search terms included combinations of Medical Subject Headings (MeSH) and keywords and terms such as "rheumatoid arthritis," "amyotrophic lateral sclerosis," "primary lateral sclerosis,", "RA and ALS comorbidity", "shared mechanisms between RA and ALS", "immunogenetic mechanisms," "inflammatory pathways," "autoimmunity," "neurodegeneration," "cytokines," "TNF-alpha," "IL-6," "IL-1β," "NF-κB," "autoantibodies," and "neuroinflammation."

The search was limited to articles published in English, with no restriction on publication date. Additional references were identified by manually searching the bibliographies of relevant articles and reviews. Studies were included if they discussed the pathophysiology, immunogenetic mechanisms, or clinical overlap between RA and ALS/PLS including consideration of causal treatments such as TNF inhibitors. Case reports, case-based reviews, cohort studies, and studies exploring mechanism of action were prioritised.

Review of Shared Inflammatory Pathways and Cytokines

Both Rheumatoid Arthritis and ALS are characterised by the shared dysregulation of key inflammatory pathways (Figure 1) including TNF-α, the interleukins IL-6, IL-1β, and NF-κB. TNF- α is known to drive synovial inflammation and joint destruction in RA, while in ALS it contributes to degeneration of motor neurons and neuroinflammation [7,8]. The cytokine IL-6, plays an instrumental role in RA, promoting synovitis and systemic inflammation and has also been implicated in glial activation and motor neuron injury in ALS [5,9]. IL-1β is involved in cartilage degradation in RA and also plays a pivotal role in neuroinflammation and neuronal apoptosis in ALS [10].

The nuclear factor-kappa B (NF-κB) pathway, a key inflammatory inducer, is activated in both RA and ALS. In RA, NF-κB activation drives the production of pro-inflammatory cytokines and matrix metalloproteinases, contributing to synovial inflammation and joint destruction. In ALS, NF-κB exacerbates motor neuron damage and has been implicated in the pathogenesis of familial ALS. Additionally, numerous environmental risk factors associated with ALS are known to stimulate NF-κB, further underscoring its central role in disease progression [11,12].

Autoantibodies and Immune Dysregulation

Autoantibodies like rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPS) such as anti-CCP are hallmark features of RA. While autoantibodies are not typically associated with ALS, recent studies have identified the presence of autoantibodies against neuronal antigens in some ALS patients, suggesting a potential autoimmune component to the disease [13]. B-cell dysregulation is a key feature and has also been observed in ALS, although therapies targeting B-cells such as rituximab have shown limited efficacy in ALS [14].

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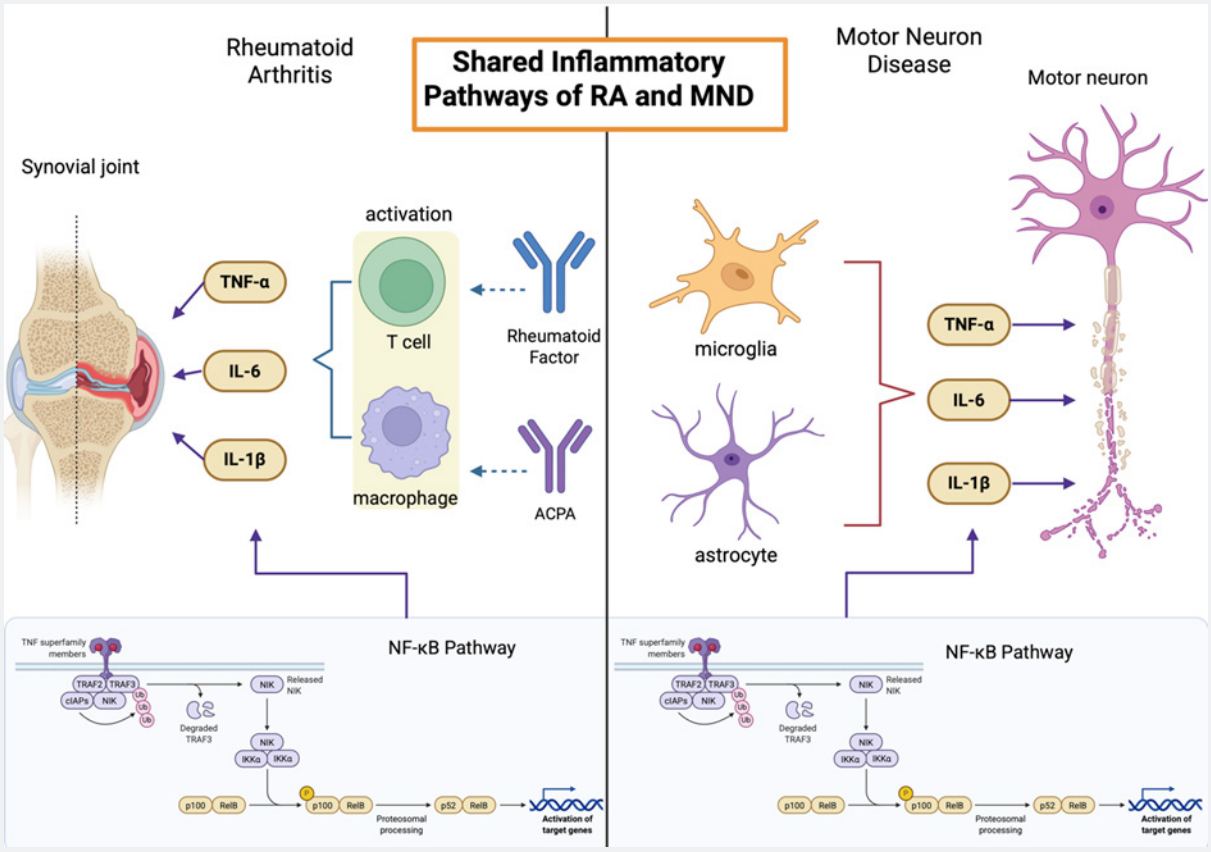

Figure 1: Shared inflammatory pathways in rheumatoid arthritis (RA) and amyotrophic lateral sclerosis (ALS), highlighting overlapping mechanisms including TNF-α, IL-6, and NF-κB. Colour coding: blue = RA, green = ALS, purple = shared. Created with BioRender.com.

Genetic Predispositions

Shared genetic factors such as polymorphism in the HLA region have been implicated in both RA and ALS. For example, HLA-DRB1 alleles are associated with increased susceptibility to RA, while certain HLA variants such as an increased HLA-B35 and a lower HLA-A9 and HLA-DR4 level were observed in ALS participants [15]. Mutations such as TARDBP and SOD1 which are implicated in ALS have also been associated with inflammatory pathways, suggesting a potential link between neurodegeneration and immune dysregulation [16-18].

Neuroinflammation and Blood-Brain Barrier Dysfunction

Systemic inflammation in RA has been implicated in disrupting the blood-brain barrier (BBB), a critical protective interface that regulates the passage of molecules and immune cells into the central nervous system (CNS). In RA, chronic elevation of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β, can compromise BBB integrity, facilitating the infiltration of immune cells and autoantibodies into the CNS [19]. This breach of the BBB may contribute to CNS complications in RA, such as cognitive dysfunction or neuropathy, and could potentially exacerbate neurodegeneration in conditions like amyotrophic lateral sclerosis (ALS).

In ALS, neuroinflammation is a hallmark of disease progression, driven primarily by microglial activation and astrogliosis. Activated microglia releases pro-inflammatory cytokines, such as TNF-α and similarly to RA, IL-1β, which contribute to motor neuron injury and neuronal apoptosis [20]. Astrocytes, which normally work to support neuronal function, become reactive in ALS, further amplifying neuroinflammation and creating a toxic environment for motor neurons [21]. The overlap in inflammatory markers between RA and ALS, such as TNF-α and IL-6, suggests a potential interplay between systemic inflammation in RA and neuroinflammation in ALS [22-24]. For instance, systemic inflammation in RA could exacerbate neuroinflammatory processes in ALS, accelerating motor neuron degeneration [5].

Additionally, the disruption of the BBB in RA may allow systemic inflammatory mediators to directly influence the CNS microenvironment, potentially worsening neuroinflammation in ALS. This bidirectional relationship between systemic and

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neuroinflammation highlights the need for further research into how chronic inflammatory conditions like RA may influence the onset or progression of neurodegenerative diseases like ALS. Understanding these mechanisms could provide insights into shared therapeutic targets, such as modulating TNF-α or IL-6 signaling, to mitigate both systemic and neuroinflammation [25].

TNF-A Inhibitors and the Risk of Developing ALS

TNF-α inhibitors, such as etanercept, are widely used in rheumatoid arthritis (RA) for their anti-inflammatory effects. However, concerns have been raised about their potential association with amyotrophic lateral sclerosis (ALS). As of December 2012, 25-31 cases of ALS were reported to EudraVigilance in patients treated with TNF-α inhibitors [26]. TNF-α plays a dual role in the central nervous system (CNS), exerting neuroprotective effects at low levels but promoting neurotoxicity and motor neuron degeneration at high concentrations. In ALS, elevated TNF-α levels contribute to microglial activation, astrogliosis, and motor neuron apoptosis.

Systemic suppression of TNF-α in RA may disrupt this balance, potentially impairing neuroprotection or exacerbating neuroinflammation. Disruption of the blood-brain barrier (BBB) in RA could further facilitate CNS entry of TNF-α inhibitors, amplifying their effects. Despite these concerns, some studies, such as [27], found no significant association between TNF-α inhibitors and ALS, highlighting the need for further research. Factors such as genetic predisposition, treatment duration, and pre-existing neuroinflammation may influence individual risk. This evidence underscores the importance of monitoring RA patients on TNF-α inhibitors for early signs of neurodegeneration and exploring alternative therapies for high-risk individuals.

Discussion

The co-occurrence of RA and ALS in this 71-year-old female patient raises important questions about the potential interplay between autoimmune and neurodegenerative diseases. While RA and ALS have traditionally been viewed as distinct entities, this case highlights the diagnostic and therapeutic challenges posed by their rare overlap, especially in the context of chronic inflammation and long-term biologic use. The patients' progressive neurological symptoms, including slurred speech and gait disturbances, may have presented a diagnostic challenge due to overlapping symptoms with RA, such as fatigue and joint pain. Neurophysiological studies ultimately confirmed a diagnosis of primary lateral sclerosis (PLS), a rare variant of ALS, supported by findings of axonal changes, fasciculations and myokymic potentials. Her extensive treatment history including methotrexate, etanercept, rituximab, tocilizumab, Upadacitinib and stem cell therapy raises important questions about the potential role of these therapies in neurodegeneration. This case aligns with emerging evidence suggesting shared immunogenetic and pathophysiologic mechanisms between RA and ALS.

Notably, the patient's long-term use of etanercept is particularly relevant given reports of an increased risk of ALS associated with TNF-α inhibitors [26]. The differential diagnosis for this patient may have included other neurodegenerative conditions such as multiple sclerosis and spinal muscular atrophy. However, the absence of sensory deficits, normal MRI findings and presence of fasciculations and myokymic potentials on electromyography supported a diagnosis of PLS. This diagnostic process highlights the importance of thorough investigation in RA patients presenting with progressive neurological symptoms, particularly for those with a history of long-standing inflammation and biologic therapy.

The implications of this case extend beyond the individual patient, contributing to the growing body of evidence on the intersection between autoimmunity and neurodegeneration. While some studies have found no significant association between TNF-α inhibitors and ALS [27], the potential risks warrant further investigation, particularly in patients with long standing RA and additional risk factors for neurodegeneration. This case also highlights the need for biomarkers, such as neurofilament light chain, [28], or specific autoantibodies (e.g., anti-neuronal antibodies or ACPA), to identify RA patients at risk of developing ALS, enabling earlier diagnosis and intervention.

The strengths of this case report include its detailed clinical and diagnostic investigations, which provide valuable insights into the challenges of diagnosing and managing coexisting RA and ALS/PLS. However, limitations should be considered. The rarity of this association limits the ability to draw general conclusions from findings, and the patient's history of multiple biologic and non-biologic therapies complicates the identification of causative factors. Additionally, the lack of long-term follow-up data restricts our ability to draw definitive conclusions about the progression and prognosis of her condition.

Conclusion and Future Perspectives

This case highlights the rare co-occurrence of RA and ALS, emphasizing the diagnostic and therapeutic challenges posed by overlapping and neurodegenerative conditions. The patient's history of long-standing RA and treatment with TNF- α inhibitors such as etanercept raises important questions about the potential role of chronic inflammation and biologic use in neurodegeneration. Whilst the evidence remains inconclusive, the case contributes to the growing body of literature suggesting shared immunogenetic and pathophysiologic mechanisms between RA and ALS [5].

Future research should focus on clarifying the mechanisms underlying this potential association, including the role of systemic inflammation, blood-brain barrier disruption and genetic predispositions. Longitudinal studies and investigations exploring potential shared mechanisms of these diseases are essential to explore the interplay between autoimmunity and neurodegeneration. Targeted therapies that address both

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autoimmune and neurodegenerative processes, such as IL-1β inhibitors, NF-κB pathway modulators, or novel neuroprotective agents, represent promising avenues for future research. By addressing these gaps, this case may inform clinical protocols and stimulate further inquiry into the intersection between autoimmunity and neurodegeneration, ultimately improving outcomes for patients with coexisting conditions.

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