Chronic Inflammation With a Focus on CRMO and other Autoimmune Disorders

Maritssia Abdelshiheed[1], Arushi Gupta[2], Jalyn Huang[3#]

[1] Woodbridge High School
[2]Irvine High School
[3]Irvine High School
[#]Advisor

Abstract

Chronic inflammation is a central feature in many disorders, ranging from autoimmune diseases to autoinflammatory conditions such as Chronic Recurrent Multifocal Osteomyelitis (CRMO).

The main findings emphasize that chronic immune dysregulation plays a critical role in disease development, with CRMO serving as an important example of how innate immune dysfunction manifests clinically. Current diagnostic approaches, such as whole-body MRI, and available treatment options, including nonsteroidal anti-inflammatory drugs and biologic therapies, have improved outcomes but remain limited in scope.

By situating CRMO within the larger framework of inflammation and immune-mediated disease, this research underscores the importance of continued investigation into underlying mechanisms, improved diagnostic strategies, and novel therapeutic approaches.

This paper explores the fundamental components of the immune system, the processes of inflammation, and the progression from acute to chronic states that can drive disease.

Introduction

Inflammation is one of the body's most vital defense mechanisms—a built in response that helps protect and heal when tissues are injured or threatened. (1)Under normal conditions, critical functions include to contain damage, fight off infection, and restore balance. However, when this response becomes dysregulated or persists beyond its useful purpose, it can lead to what is known as chronic inflammation—a prolonged, low-grade immune activation that can damage tissues and disrupt normal physiological functions over time. (2)

Chronic inflammation is now understood to play a key role in the development and progression of numerous diseases, including cardiovascular disorders, autoimmune conditions, metabolic syndromes, and certain musculoskeletal pathologies. (3) Its presence may not always be obvious, yet its long-term effects can be significant and, in many cases, debilitating.

One rare but increasingly recognized condition driven by chronic inflammation is Chronic Recurrent Multifocal Osteomyelitis (CRMO)—a non-infectious, autoinflammatory bone disease primarily seen in children and adolescents. (4)Unlike typical forms of osteomyelitis, which are caused by bacterial infection, CRMO arises without any identifiable pathogen. It is characterized by episodes of bone pain and localized inflammation that can occur in multiple sites and often recur over time. (5)
Although CRMO remains a relatively rare diagnosis, growing awareness and improvements in imaging and diagnostic techniques have led to earlier recognition and better management of the condition. (6)This review examines chronic inflammation and its role in the development of autoimmune and autoinflammatory diseases, with a particular focus on Chronic Recurrent Multifocal Osteomyelitis (CRMO). By exploring these conditions in depth, the goal is to provide a clearer understanding of their underlying mechanisms, clinical features, and current approaches to diagnosis and treatment. As research continues to evolve, there is increasing potential for more accurate recognition, earlier intervention, and improved care for individuals affected by these complex immune-driven disorders.

The Components of the Immune System

The human immune system is a remarkable network of interconnected organs, specialized cells, and molecular messengers that work tirelessly to defend the body against external threats and maintain internal stability(7). Fundamentally, it operates through two complementary arms: the *innate immune system and the adaptive immune system*, each performing distinctive yet cooperative roles.

The innate immunity serves as the body's immediate, first-response defense mechanism. This arm includes physical obstacles such as the skin and mucosal membranes, which act as primary barriers against microbial invasion.(8) Internally, it comprises *phagocytosis cells* like macrophages ad neutrophils, as well as dendritic cells that help process and present antigens. These cells recognize general molecular signatures of danger—termed pathogen—associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs)—through pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs)(9). Once activated, these receptors engage intracellular signaling cascades—such as NF-kB pathways—leading to production of cytokines and chemokines that recruit additional immune participants and shape the inflammatory response.

Beyond cell-based responses, innate immunity also includes soluble components that operate without cellular mediation. The *complement system*, a cascade of plasma proteins, enhances inflammation, opsonizes pathogens for *phagocytosis*, and forms complexes that can directly perforate bacterial membranes(10). *Antimicrobial peptide and acute-phase proteins*—produced during an inflammatory state—contribute to early microbial control and modulation of the inflammatory environment.

In contrast, adaptive immunity provides highly specific and enduring protection tailored to particular pathogens (11). B lymphocytes generate antibodies that neutralize or mark pathogens for destruction. T lymphocytes have differentiated roles: helper T cells (CD4+) assist other immune cells, while cytotoxic T cells (CD8+) directly destroy infected or malignant cells. A
hallmark feature of adaptive immunity is immunological memory, enabling faster and more potent responses upon repeat exposure to the same antigen (12). Though adaptive responses take longer to mobilize initially, they are indispensable for long-term immunity.

The interplay between the innate and adaptive branches ensures a robust defense system: the innate arm provides rapid initial containment and signals, while the adaptive system refines and sustains the response. This collaboration preserves host health while controlling inflammation through precise and measured action.

What is Inflammation

Inflammation is the body's highly regulated reaction to potentially harmful stimuli—including pathogens, injured cells, or irritants—and aims to eradicate the source of damage while initiating repair. At the earliest stage, acute inflammation occurs swiftly and is characterized by increased blood flow (vasodilation) and enhanced vascular permeability, resulting in localized heat, redness, swelling, and pain (13). Immune cells—especially neutrophils and mast cells—migrate to the affected site under the influence of chemotactic signals, contributing to pathogen elimination and cleanup of damaged tissue.

When the initial threat is contained and inflammatory mediators decline, acute inflammation typically resolves, leading to tissue repair and restoration of normal function. However, if the triggering factor persists—such as in prolonged infection or immune dysregulation—or if resolution mechanisms fail, the process may evolve into chronic inflammation (14). This prolonged immune activation is characterized by infiltration of mononuclear cells (like macrophages and lymphocytes), continued production of inflammatory mediators, and in some cases, tissue fibrosis. Unlike acute inflammation, which exhibits overt clinical signs, chronic inflammation can progress insidiously yet drive long-term pathology.

At the molecular level, chronic inflammation involves persistent release of pro-inflammatory cytokines such as interleukins and TNF, production of reactive oxygen and nitrogen species, and upregulation of matrix metalloproteinases—enzymes that degrade extracellular matrix. (15). These factors together can disrupt normal tissue architecture and contribute to the development of disorders such as atherosclerosis, type 2 diabetes, autoimmune conditions, and inflammatory bone diseases.

Diseases rooted in immune dysfunction fall into two main categories. Autoimmune disorders

occur when the adaptive immune response mistakenly targets the body's own tissues—for example, in rheumatoid arthritis or systemic lupus erythematosus—driven by autoreactive T cells or autoantibodies. (16). In contrast, autoinflammatory conditions—such as CRMO—arise from
intrinsic malfunction within the innate immune system, resulting in repeated episodes of sterile inflammation without presence of specific autoantibodies or adaptive immune activation.

While inflammation is essential for survival, its chronic form—especially when driven by unregulated innate immune activity—can become harmful (17). Autoinflammatory diseases illustrate how innate immune dysfunction may result in recurrent, episodic inflammation without the involvement of pathogens or adaptive immune factors.

A poignant illustration is Chronic Recurrent Multifocal Osteomyelitis (CRMO), a condition in which sterile inflammation localizes to bone (18). Recurrent episodes of discomfort and inflammation in multiple skeletal regions in children demonstrate how chronic immune misdirection can yield clinical syndromes that challenge both diagnosis and management. With this understanding of underlying immunity and inflammation, we now turn to a detailed analysis of CRMO—its manifestations, origins, diagnostic hurdles, and treatment strategies.

What is CRMO

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a rare pediatric autoinflammatory disorder, recognized as a subset of Chronic Nonbacterial Osteomyelitis (CNO) (5). It manifests through episodic, often symmetrical, sterile bone inflammation at multiple anatomical sites. CRMO primarily impacts children and adolescents, emerging between ages eight and fourteen (19). Commonly affected bones include the long bones—such as the femur and tibia—as well as the clavicle, spine, pelvis, and occasionally craniofacial bones. Clinically, patients endure recurring bouts of intense bone pain and swelling that can impair mobility and daily activities (20).These flares typically alternate with periods of remission, but the unpredictability and duration of symptoms can be distressing. Although CRMO is not caused by infection, it may mimic infectious osteomyelitis or malignancy, often leading to diagnostic delays and emotional burden for families.

Etiology and Proposed Causes

The exact pathogenesis of CRMO remains an active area of investigation, but current evidence implicates dysregulation in the innate immune system, particularly in the pathways that regulate sterile inflammation (21). Observations of elevated pro-inflammatory cytokines and increased

activity of components like the inflammasome in immune cells—especially monocytes—suggest an intrinsic overactivation without infectious trigger. Further molecular studies have highlighted dysregulation in signaling pathways such as TLR4/MAPK, which appear to exacerbate inflammatory cascades in CRMO (20). Genetic predisposition is also suspected; familial clustering and overlaps with syndromes such as SAPHO (Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis) reinforce the idea of heritable susceptibility and shared immunopathological mechanisms.

Diagnosis

Diagnosing CRMO is challenging due to the lack of definitive biomarkers. The process generally involves ruling out infectious causes and malignancies. Laboratory evaluations may reveal mildly elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)—indicative of an inflammatory response—but these parameters are nonspecific (21). Notably, autoantibodies are absent, which helps differentiate CRMO from autoimmune conditions. The most valuable diagnostic tool is whole-body magnetic resonance imaging (WBMRI), which allows visualization of both symptomatic and asymptomatic lesions (22). MR imaging often reveals characteristic patterns, such as metaphyseal long-bone edema or vertebral involvement, even before symptoms emerge (5). This makes WBMRI critical not only for diagnosis but also for monitoring disease progression and treatment response. When imaging and clinical presentation remain ambiguous, bone biopsy may be warranted to definitively exclude infection or neoplasm.

Treatment

Management of CRMO is centered around alleviating symptoms, controlling sterile inflammation, and preventing structural damage to the skeleton. Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered first-line treatment and are often sufficient for patients with mild to moderate disease; naproxen is commonly employed (23). In more severe or recalcitrant cases—particularly with vertebral involvement—additional therapies may be necessary. Bisphosphonates, known for their bone-protective properties, can help suppress inflammatory bone resorption and are particularly useful for spinal lesions. Biologic agents, specifically TNF-α inhibitors, have demonstrated effectiveness in cases unresponsive to standard treatments and in those with concurrent inflammatory syndromes. Moreover, they offer a targeted approach by directly modulating key inflammatory pathways (22). Additional options—such as corticosteroids or disease-modifying antirheumatic drugs (DMARDs) like methotrexate or sulfasalazine—may be considered for patients with persistent or relapsing disease. Due to their side effect profiles, these are typically used judiciously. Given the chronic and variable nature of CRMO, continuous evaluation and management are essential. Adopting an integrated care

model—involving specialists from rheumatology, radiology, orthopedics, and rehabilitation—supports comprehensive treatment and addresses both physical and emotional wellness.

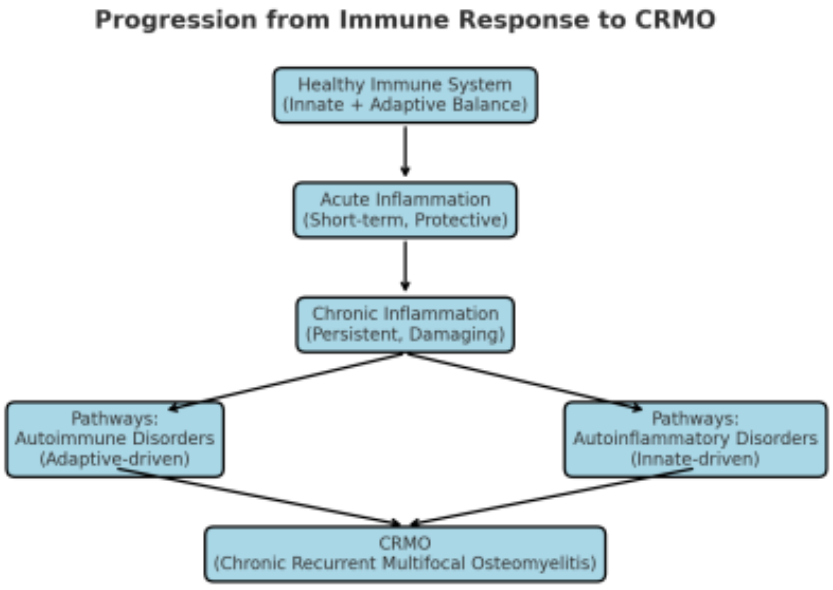
Conclusion

The study highlights the complex yet coordinated nature of the immune system, its role in inflammation, and the consequences of chronic immune dysregulation. When acute inflammation fails to resolve, it can develop into persistent and damaging states that underlie many chronic diseases, including autoinflammatory conditions such as Chronic Recurrent Multifocal Osteomyelitis (CRMO) (19). By examining CRMO specifically, the research underscores how innate immune dysfunction can manifest as recurring sterile bone inflammation, resulting in a disorder that remains difficult to diagnose and treat effectively. Understanding these processes is vital, as they represent not only a medical challenge but also a profound human burden for affected children and their families.

While this research provides a comprehensive overview, much remains unclear regarding the precise mechanisms driving CRMO and other chronic inflammatory disorders. These gaps emphasize the continued importance of advancing research in immunology and inflammatory disease. The study is important because it draws attention to the pressing need for earlier diagnosis, improved therapies, and broader awareness of conditions like CRMO, which are often overlooked due to their rarity.

Future work should expand on these findings by pursuing deeper exploration of immune pathways, refining diagnostic tools, and developing more targeted interventions that can balance efficacy with safety. Such efforts will not only benefit individuals living with CRMO but also enhance broader understanding of chronic inflammation and autoimmune disease as a whole

Figure 1. Progression from a healthy immune system to Chronic Recurrent Multifocal Osteomyelitis.



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