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Review Article

Adult-onset Still's disease: a comprehensive review of cutaneous manifestations and their correlation with rheumatologic disease activity

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ABSTRACT

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder characterized by spiking fevers, arthralgia, leukocytosis and evanescent cutaneous eruptions. The dermatologic manifestations of AOSD are not only pathognomonic but also serve as critical biomarkers for disease activity and prognosis. This article systematically reviews the clinical and histopathological features of AOSD-associated dermatologic lesions, emphasizing their correlation with systemic inflammation and rheumatologic disease severity. We explore the underlying immunopathogenic mechanisms, including the role of proinflammatory cytokines such as interleukin (IL)-1β, IL-6 and IL-18, in driving both cutaneous and systemic manifestations. Furthermore, we discuss the diagnostic challenges posed by atypical presentations and the utility of skin biopsies in differentiating AOSD from mimickers such as drug reactions, viral exanthems and other rheumatic diseases. By integrating current evidence, this review aims to enhance clinicians' ability to recognize, diagnose and monitor AOSD through its dermatologic hallmarks.

Keywords: Adult-onset still's disease, Cutaneous manifestations, Dermatopathology, Disease activity biomarkers, Evanescent rash, Interleukin-1β, Interleukin-6

INTRODUCTION

Adult-onset still's disease (AOSD) is a multisystemic autoinflammatory syndrome of unknown etiology, first described by Bywaters in 1971 as the adult counterpart of juvenile idiopathic arthritis (JIA). Despite its rarity, AOSD presents with a distinct clinical trial of quotidian fevers, polyarthritis and a characteristic salmon-pink maculopapular rash, often accompanying disease flares. The cutaneous manifestations of AOSD are of particular diagnostic and prognostic significance, as they frequently parallel systemic inflammation and may guide therapeutic decision-making.[1,2] The classic evanescent rash of AOSD typically appears during febrile episodes, presenting as non-pruritic, erythematous macules or papules distributed over the trunk and proximal extremities. Histopathologically, these lesions demonstrate a superficial perivascular infiltrate of neutrophils and mononuclear cells, devoid of vasculitic changes. However, atypical dermatologic presentations such as persistent plaques, urticarial lesions or even prurigo-like eruptions have been documented, complicating the diagnostic paradigm.[1,2]

Emerging evidence underscores the pivotal role of cytokine dysregulation, particularly the IL-1/IL-6/IL-18 axis, in linking cutaneous inflammation to systemic disease activity. Serum ferritin elevation, a hallmark of AOSD, further reflects macrophage activation and correlates with both cutaneous and articular severity. This

review synthesizes current knowledge on the dermatologic-rheumatologic interplay in AOSD, advocating for a multidisciplinary approach to optimize diagnostic accuracy and therapeutic outcomes. By elucidating the cutaneous signatures of AOSD, we aim to bridge gaps in clinical recognition and underscore the skin as a window to systemic disease dynamics.[1]

EPIDEMIOLOGY

Adult-onset still's disease (AOSD) is a rare systemic autoinflammatory disorder with an estimated annual incidence of 0.16 to 0.62 cases per 100,000 population, though this figure may be underestimated due to diagnostic challenges and heterogeneous presentations.

Epidemiological studies suggest a bimodal age distribution, with peak onset occurring between 16–25 years and a second, smaller peak in individuals aged 36–46 years, though cases have been reported across all adult age groups. There is no definitive gender predilection, with some studies indicating a slight female predominance (female-to-male ratio ~1.1–2:1), while others report near-equal distribution.[3]

Geographically, AOSD appears to affect populations worldwide, though reported prevalence varies regionally, potentially due to differences in diagnostic awareness, genetic predisposition or environmental triggers. No clear racial or ethnic predilection has been established, though some studies suggest a higher incidence in Asian populations, possibly linked to genetic polymorphisms in HLA-DRB1*12 and HLA-Bw35, which have been weakly associated with disease susceptibility.[3]

Cutaneous manifestations in epidemiological context

The classic evanescent salmon-pink rash is reported in 60–90% of AOSD patients, making it one of the most common clinical features alongside fever and arthritis. However, the prevalence of cutaneous involvement may vary depending on disease subtype.[3] Systemic-predominant AOSD (marked by fever, hepatosplenomegaly and serositis) exhibits a higher frequency of rash (up to 90%), often correlating with elevated ferritin and IL-18 levels.[4]

Articular-predominant AOSD (chronic arthritis resembling rheumatoid arthritis) may present with less prominent or atypical skin lesions, contributing to delayed diagnosis.[4] A subset of patients (10–30%) develops persistent or atypical dermatologic lesions, including.

Urticarial plaques (resembling neutrophilic urticaria). Prurigo-like or lichenoid eruptions. Linear or flagellate erythema (rare but highly suggestive of AOSD). These variations may reflect differences in cytokine profiles (e.g., IL-1β vs. IL-6 dominance) or genetic background, warranting further epidemiological stratification.[4]

Mortality and comorbidity considerations

While AOSD is generally self-limiting or controllable with immunosuppression, severe cases may develop life-threatening complications, including. Macrophage activation syndrome (MAS) (occurring in 10–15% of cases, with mortality up to 20%). Diffuse intravascular coagulation (DIC). Fulminant hepatitis.

Cutaneous manifestations, particularly persistent or necrotizing lesions, may signal higher disease severity and correlate with increased risk of systemic complications. Long-term follow-up studies indicate that ~30–50% of patients experience chronic or relapsing disease, with cutaneous flares often preceding systemic exacerbations.[4]

Conclusion: the epidemiological significance of dermatologic involvement

The epidemiology of AOSD underscores its heterogeneity, with cutaneous manifestations serving as both diagnostic markers and potential predictors of disease behavior.

Future population-based studies incorporating molecular profiling (e.g., cytokine signatures, HLA associations) could refine subclassification and improve prognostic accuracy. Recognizing the prevalence and diversity of AOSD-related skin lesions is essential for timely diagnosis, particularly in cases lacking classic systemic features.[5]

PATHOPHYSIOLOGY

Adult-onset Still's disease (AOSD) is a multifactorial autoinflammatory disorder characterized by a dysregulated innate immune response, leading to excessive cytokine production and systemic inflammation. The pathophysiology involves a complex interplay of genetic predisposition, environmental triggers and immune dysregulation, with cutaneous manifestations serving as a visible reflection of underlying immunological disturbances.[5]

Innate immune activation and cytokine storm

The hallmark of AOSD is a hyperinflammatory state driven by overactivation of the innate immune system, particularly involving macrophages, neutrophils and dendritic cells. Key cytokines implicated in AOSD pathogenesis include.[5]

Interleukin-1β (IL-1β)

A central mediator of systemic and cutaneous inflammation, IL-1β promotes fever, neutrophil recruitment and endothelial activation. Its overexpression correlates with evanescent rash development and disease flares.[5]

Interleukin-6

Drives acute-phase reactants (e.g., CRP, ferritin) and contributes to arthralgia, fever and persistent cutaneous lesions. Elevated IL-6 levels are associated with chronic arthritis and refractory disease.[5]

Interleukin-18

Strongly linked to macrophage activation syndrome (MAS), IL-18 promotes IFN-γ production and correlates with severe cutaneous and systemic involvement.[5]

Tumor necrosis factor-alpha

Contributes to synovial inflammation and may play a role in treatment-resistant skin eruptions.[5] This cytokine storm results in widespread inflammation, explaining the febrile episodes, serositis and transient rash that typify AOSD.[5]

Role of NLRP3 inflammasome and pyroptosis

The NLRP3 inflammasome, a key component of innate immunity, is aberrantly activated in AOSD, leading to caspase-1-mediated cleavage of pro-IL-1β into its active form. This process induces pyroptosis, a proinflammatory form of cell death that amplifies cytokine release.[6]

Cutaneous implications

Inflammasome activation in keratinocytes and dermal dendritic cells may contribute to the characteristic non-pruritic, salmon-pink rash, with histopathology revealing perivascular neutrophilic infiltrates without true vasculitis.[6]

Systemic correlation

Inflammasome hyperactivity correlates with higher disease activity scores (e.g., systemic score, ferritin levels) and more severe organ involvement.[6]

Neutrophil extracellular traps and skin inflammation

Recent studies suggest that dysregulated neutrophil activation and NETosis play a role in AOSD-related tissue damage. Excessive NET release may. Stimulate type I interferon pathways, exacerbating systemic inflammation. Contribute to persistent or atypical cutaneous lesions (e.g., urticarial plaques, neutrophilic dermatosis-like eruptions).[6]

Genetic and environmental triggers

While no single genetic cause has been identified, certain HLA alleles (e.g., HLA-DRB1*12, HLA-Bw35) are weakly associated with AOSD susceptibility. Environmental factors, including viral infections (e.g., EBV, CMV, parvovirus B19), may trigger disease onset in genetically predisposed individuals via molecular mimicry or bystander immune activation.[6]

Cutaneous-rheumatological correlation: the skin as a disease activity mirror

The transient nature of the AOSD rash aligns with fluctuating cytokine levels, making it a useful clinical biomarker.

Evanescent rash during fever spikes→Reflects acute IL-1β/IL-6 surge.[6] Persistent or pruritic lesions→May indicate chronic IL-18-driven inflammation or secondary MAS.[6] Linear/flagellate erythema→Suggests severe endothelial activation.[6] Histopathological findings (e.g., dermal neutrophilia without vasculitis) further differentiate AOSD from mimickers like cutaneous lupus or vasculitis.[6]

The pathophysiology of AOSD underscores a continuum between autoinflammation and autoimmunity, with cutaneous manifestations providing critical diagnostic and prognostic clues. Emerging therapies targeting IL-1β (anakinra, canakinumab), IL-6 (tocilizumab) and JAK/STAT pathways highlight the importance of personalized treatment based on dominant cytokine profiles. Future research should explore skin-specific biomarkers to refine disease monitoring and therapeutic strategies.[6]

CLINICAL MANIFESTATIONS

Adult-onset still's disease (AOSD) presents as a complex multisystemic inflammatory disorder characterized by a constellation of clinical features that evolve through different disease phases. The classic triad of quotidian fever, arthritis and evanescent cutaneous eruption represents the hallmark presentation, though the full clinical spectrum encompasses a wide array of systemic and dermatologic manifestations that frequently correlate with disease activity and prognosis.[6]

The febrile component typically manifests as a spiking high-grade temperature (>39°C) occurring once or twice daily, often in the late afternoon or evening, followed by rapid defervescence. This fever pattern reflects the underlying cytokine storm, particularly the pulsatile release of interleukin (IL)-1β and IL-6.

During these febrile episodes, approximately 75-90% of patients develop the pathognomonic cutaneous manifestation - a transient, non-pruritic, salmon-pink macular or maculopapular eruption with a characteristic distribution favoring the trunk and proximal extremities. The evanescent nature of this exanthem, which typically fades with fever resolution, mirrors the fluctuating levels of proinflammatory cytokines and serves as a visible biomarker of disease activity.[6] Musculoskeletal involvement constitutes another cardinal feature, presenting as severe polyarthralgias or polyarthritis that

typically affects large joints (knees, wrists and ankles) in a symmetrical pattern. The articular manifestations frequently demonstrate a temporal progression from intermittent arthralgias during disease flares to a potentially destructive chronic arthritis resembling rheumatoid arthritis in approximately 30% of cases. This progression correlates with the transition from innate immune activation to adaptive immune responses, with corresponding changes in cytokine profiles from IL-1β/IL-18 dominance to IL-6/IL-17 predominance.[7]

The dermatologic manifestations of AOSD extend beyond the classic evanescent rash, with various persistent or atypical cutaneous findings providing important clinical clues. Approximately 20-30% of patients develop persistent pruritic papules or plaques that may demonstrate a lichenoid or urticarial morphology. These lesions often correlate with more severe systemic inflammation and elevated IL-18 levels, serving as cutaneous markers of disease chronicity. Less common but highly suggestive dermatologic presentations include linear or flagellate erythema patterns, which may reflect direct cytokine-mediated endothelial activation or neutrophil-mediated keratinocyte injury.[7]

Systemic manifestations frequently accompany the cutaneous and articular features, with lymphadenopathy (65%), hepatosplenomegaly (50-70%) and serositis (30%) representing common extracutaneous findings. The presence of these systemic features often parallels the intensity of cutaneous involvement, with more extensive or persistent skin lesions frequently observed in patients with marked visceral organ involvement. Laboratory abnormalities, including leukocytosis with neutrophilia, markedly elevated ferritin levels (>1000 ng/mL) and elevated liver enzymes, further reflect the systemic inflammatory burden and frequently correlate with cutaneous disease activity.[7]

The clinical course of AOSD demonstrates considerable heterogeneity, with patterns ranging from self-limited monophasic illness (30%) to intermittent polycyclic flares (35%) or persistent chronic disease (35%). Cutaneous manifestations often provide early prognostic clues, as patients who develop persistent or atypical skin lesions tend to experience more protracted disease courses with higher rates of articular damage.

Furthermore, the appearance of new or changing cutaneous findings may herald disease complications, such as the development of macrophage activation syndrome, which frequently presents with hemorrhagic or necrotic skin lesions in conjunction with worsening systemic symptoms.[8] The intricate relationship between cutaneous manifestations and systemic disease activity underscores the importance of thorough dermatologic evaluation in AOSD management. The temporal association of skin eruptions with fever spikes, their characteristic morphology and distribution and their evolution over time all provide valuable insights into disease pathophysiology and progression. As our understanding of the cytokine networks driving both cutaneous and systemic inflammation in AOSD continues to evolve, these dermatologic features are increasingly recognized not merely as diagnostic criteria, but as external manifestations of internal inflammatory processes that can guide therapeutic decision-making and prognostic assessment.[8,9]

DIAGNOSTIC APPROACH

The diagnosis of adult-onset Still's disease (AOSD) represents a significant clinical challenge, requiring a meticulous synthesis of clinical, laboratory, histopathological and imaging findings while systematically excluding numerous mimickers. This complex diagnostic process hinges upon recognizing the characteristic triad of spiking fevers, arthritis and pathognomonic cutaneous manifestations, while simultaneously evaluating their correlation with systemic inflammatory activity and rheumatologic disease progression.[9,10]

Clinical diagnostic criteria and the pivotal role of dermatologic manifestations

Current diagnostic frameworks, including the Yamaguchi and Fautrel criteria, emphasize the primacy of cutaneous findings in establishing an AOSD diagnosis. The evanescent salmon-pink macular or maculopapular eruption - appearing concomitantly with fever spikes and demonstrating a predilection for the trunk and proximal extremities-carries particular diagnostic weight. This transient eruption, often described as "dermatologic pyrexia," reflects the underlying cytokine storm, with its intensity frequently paralleling serum levels of IL-1β, IL-6 and IL-18. Dermatologists and rheumatologists must maintain heightened awareness of atypical cutaneous presentations, including persistent urticarial plaques, prurigo-like lesions and the pathognomonic (though rare) flagellate erythema pattern, all of which may represent cutaneous biomarkers of specific cytokine profiles or disease subtypes.[10]

Laboratory investigations and cutaneous-inflammatory correlations

The laboratory workup for AOSD reveals characteristic though nonspecific inflammatory markers that frequently correlate with cutaneous disease activity. Marked hyperferritinemia (>1000 ng/ml), particularly when accompanied by a glycosylated ferritin fraction <20%, demonstrates significant specificity for AOSD and often parallels the severity of cutaneous involvement. Leukocytosis with neutrophilia (≥80% granulocytes), elevated C-reactive protein and abnormal liver function tests collectively reflect the systemic inflammatory burden, with their degree of elevation frequently mirroring the extent and persistence of dermatologic

findings. Emerging biomarkers, including serum IL-18 levels and S100 protein panels, show promise in correlating specific cutaneous phenotypes with disease prognosis and therapeutic response.[11]

HISTOPATHOLOGICAL EVALUATION OF CUTANEOUS LESIONS

When diagnostic uncertainty persists, cutaneous biopsy provides valuable diagnostic information. Characteristic histopathological features include a superficial perivascular infiltrate of neutrophils and mononuclear cells without true leukocytoclastic vasculitis, corresponding to the clinically observed evanescent rash. More persistent lesions may demonstrate interface dermatitis or dermal neutrophilia, while urticarial variants often show marked edema with mixed inflammatory infiltrates. These histologic patterns not only aid in distinguishing AOSD from cutaneous mimickers but may also provide prognostic information, as certain patterns correlate with disease chronicity and treatment resistance.[11]

Advanced imaging and multimodal assessment

Musculoskeletal ultrasound and magnetic resonance imaging frequently reveal synovitis, tenosynovitis or periarticular inflammation that correlates with both articular symptoms and cutaneous disease activity. (18F) FDG-PET/CT imaging has emerged as a valuable tool for assessing systemic inflammatory burden, often demonstrating diffuse lymph node and spleen uptake that parallels the intensity of both systemic and cutaneous manifestations.[11]

Differential diagnosis: the cutaneous clue to distinguishing mimickers

The diagnostic process necessitates careful exclusion of infectious (particularly viral exanthems), neoplastic (especially lymphoma) and other rheumatic conditions. The temporal relationship between fever patterns and cutaneous eruptions often proves crucial - whereas AOSD's evanescent rash appears with fever spikes, the persistent erythema of cutaneous lupus or the palpable purpura of vasculitis follow different temporal patterns. Drug reactions, particularly DRESS syndrome, may mimic AOSD's cutaneous findings but typically demonstrate eosinophilia and different mucosal involvement patterns.[11]

Proposed diagnostic algorithm incorporating cutaneous features

A stepwise diagnostic approach should incorporate, Documentation of fever patterns and precise characterization of cutaneous lesions. Correlation of cutaneous findings with inflammatory markers and cytokine profiles. Histopathological evaluation of persistent or atypical lesions. Systematic exclusion of infectious, neoplastic and autoimmune alternatives. Ongoing assessment of cutaneous-rheumatologic disease correlation throughout the diagnostic process. The evolving understanding of AOSD's pathogenesis underscores the importance of viewing cutaneous manifestations not merely as diagnostic criteria but as external manifestations of internal inflammatory processes. Future diagnostic paradigms will likely incorporate molecular profiling of skin lesions to further refine classification and predict treatment responses, moving toward truly personalized management strategies for this complex autoinflammatory disorder.[11]

THERAPEUTIC MANAGEMENT

The treatment paradigm for adult-onset Still's disease (AOSD) has evolved significantly in recent years, transitioning from empirical immunosuppression to targeted biologic therapies based on our growing understanding of the disease's intricate pathophysiology. This therapeutic approach must be carefully tailored to address both the systemic inflammatory burden and the characteristic cutaneous manifestations, which frequently serve as visible biomarkers of disease activity and treatment response.[12]

First-line pharmacological interventions: targeting the cytokine cascade

Initial management typically involves high-dose glucocorticoids (prednisone 0.5-1 mg/kg/day), which remain the cornerstone of therapy for inducing rapid remission in acute systemic manifestations, including the characteristic evanescent rash. The cutaneous response to corticosteroids is often dramatic, with resolution of the salmon-pink macular eruption paralleling the decline in serum inflammatory markers.

However, the steroid-sparing effect of conventional disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate (15-25 mg weekly), is frequently employed given the chronic relapsing nature of many cases. Methotrexate demonstrates particular efficacy in the articular-predominant subtype and may improve persistent cutaneous lesions through its modulation of adenosine pathways and neutrophil function.[12]

Biologic therapies: precision targeting of key cytokines

The advent of biologic agents has revolutionized AOSD treatment, with interleukin (IL)-1 inhibition emerging as particularly effective for both systemic and cutaneous manifestations. Anakinra, a recombinant IL-1 receptor antagonist administered subcutaneously (100-200 mg daily), frequently produces rapid resolution of fever and rash, often within 24-48 hours.

This dramatic response provides compelling evidence for IL-1β's central role in driving both systemic inflammation

and cutaneous manifestations. Canakinumab, a long-acting anti-IL-1β monoclonal antibody (150-300 mg every 4-8 weeks), offers similar efficacy with more convenient dosing, particularly for patients with predominantly cutaneous-rheumatologic disease flares.[12] For patients with inadequate response to IL-1 blockade or those exhibiting IL-6-dominant profiles (characterized by prominent arthritic symptoms and elevated CRP), tocilizumab (8 mg/kg IV every 4 weeks) represents an effective alternative. The agent's impact on cutaneous manifestations is somewhat variable, with excellent control of systemic symptoms but occasional persistence of mild dermatologic findings, suggesting partial divergence in the cytokine regulation of joint versus skin inflammation.[13]

Refractory disease and emerging therapeutic options

Cases refractory to first-line biologics may benefit from inhibition of alternative pathways. Janus kinase (JAK) inhibitors, particularly tofacitinib and baricitinib, have shown promise in small case series, with improvement in both articular and persistent cutaneous lesions, likely through modulation of interferon-γ and IL-18 signaling. For patients with prominent macrophage activation syndrome (MAS) features, cyclosporine A (3-5 mg/kg/day) remains an important therapeutic option, particularly when cutaneous manifestations include hemorrhagic or necrotic components suggesting severe endothelial activation.[12,13]

Cutaneous-specific therapeutic considerations

The management of AOSD-associated dermatologic manifestations requires special consideration. While the classic evanescent rash typically responds well to systemic therapies, persistent or pruritic lesions may necessitate adjunctive approaches. Topical corticosteroids (class II-III) and calcineurin inhibitors can provide symptomatic relief for localized persistent plaques, while phototherapy (narrowband UVB) has shown benefit for chronic lichenoid or prurigo-like eruptions. Antihistamines may ameliorate pruritus but have minimal impact on the underlying inflammatory process.[12,13]

Monitoring therapeutic response: the role of cutaneous markers

Serial assessment of cutaneous manifestations provides valuable real-time data on treatment efficacy. The complete resolution of evanescent rash typically correlates with adequate cytokine suppression and predicts sustained remission, while persistent or recurrent lesions often indicate suboptimal disease control.

Dermatologic flares frequently precede systemic relapses, making regular skin examinations an essential component of long-term monitoring. Serum biomarkers, particularly ferritin and IL-18 levels, should be interpreted in conjunction with cutaneous findings to guide therapeutic adjustments.[13,14]

Novel therapeutic horizons and personalized medicine approaches

Emerging therapies targeting IL-18 (tadekinig alfa) and the NLRP3 inflammasome show considerable promise in early clinical trials, particularly for patients with refractory cutaneous manifestations. The development of cytokine-specific biosignatures, potentially derived from skin biopsy analysis, may soon enable truly personalized treatment selection based on individual patients' dominant inflammatory pathways.[14]

The comprehensive management of AOSD thus requires a multidisciplinary approach integrating rheumatologic and dermatologic expertise, with treatment strategies continuously adjusted based on the evolving interplay between cutaneous and systemic disease activity. This paradigm recognizes the skin not merely as an affected organ but as a critical window into the underlying inflammatory state and therapeutic response.[15]

CONCLUSION

Adult-onset Still's disease (AOSD) represents a fascinating clinical entity at the intersection of autoinflammatory and autoimmune disorders, where cutaneous manifestations serve as both diagnostic sentinels and therapeutic barometers. This comprehensive analysis underscores the indispensable role of dermatologic findings in unraveling the complex pathophysiology of AOSD, with the characteristic evanescent rash emerging not merely as a diagnostic criterion but as a visible manifestation of the underlying cytokine storm. The intricate correlation between cutaneous phenotypes and systemic disease activity has profound implications for clinical practice, reshaping our approach to diagnosis, monitoring and therapeutic intervention.

The dermatologic-rheumatologic continuum in AOSD reveals compelling pathophysiological insights. The temporal synchrony between fever spikes and cutaneous eruptions mirrors the pulsatile release of IL-1β and IL-6, while persistent dermatologic lesions often reflect the transition to chronic IL-18-driven inflammation. This biological continuum explains why cutaneous manifestations frequently precede systemic flares and why their morphological evolution - from classic salmon-pink macules to persistent urticarial or lichenoid plaques - may signal impending disease chronicity or complications such as macrophage activation syndrome. The skin thus emerges as an accessible organ for both diagnostic confirmation and prognostic stratification.

Modern therapeutic strategies have capitalized on these pathophysiological insights, transitioning from nonspecific immunosuppression to targeted cytokine

blockade. The dramatic response of cutaneous manifestations to IL-1 inhibition provides compelling in vivo evidence of this cytokine's central role in AOSD pathogenesis, while the variable dermatologic response to IL-6 blockade suggests more complex regulation of skin versus joint inflammation. These differential treatment responses underscore the importance of considering cutaneous phenotypes when selecting biologic therapies, potentially paving the way for phenotype-directed treatment algorithms.

Several critical knowledge gaps and future directions emerge from this synthesis

Precision medicine approaches

The development of cutaneous cytokine signatures through advanced proteomic analysis of skin biopsies may enable more accurate subclassification of AOSD variants and prediction of treatment responses.

Long-term cutaneous sequelae

Further investigation is needed into the mechanisms underlying persistent dermatologic manifestations and their association with disease chronicity, particularly the role of neutrophil extracellular traps (NETs) and endothelial dysfunction.

Biomarker discovery

The correlation between specific cutaneous phenotypes and emerging biomarkers (such as galectin-3 or S100 proteins) warrants exploration as potential tools for monitoring subclinical disease activity.

Therapeutic innovation

Clinical trials of novel agents targeting the IL-18/IFN-γ axis should incorporate detailed dermatologic assessments to evaluate their impact on both systemic and cutaneous disease components. The management of AOSD demands a truly multidisciplinary approach, with dermatologists and rheumatologists collaborating closely to interpret cutaneous signs in the context of systemic inflammation. This integrated perspective enables earlier diagnosis, more accurate assessment of disease activity and more nuanced therapeutic decisions. As our understanding of the cutaneous-systemic interface in AOSD deepens, the skin is poised to assume an increasingly prominent role - not just as a diagnostic canvas, but as a dynamic monitor of disease activity and therapeutic response.

In conclusion, AOSD epitomizes the inseparable link between cutaneous manifestations and systemic autoinflammation. The evolving recognition of dermatologic findings as mirrors of internal inflammatory processes has transformed our diagnostic and therapeutic paradigms, offering new opportunities for personalized medicine in this challenging disorder. Future research focusing on the molecular underpinnings of AOSD-associated skin lesions promises to unlock further insights into disease mechanisms and therapeutic targets, ultimately improving outcomes for patients across the spectrum of this multifaceted condition.

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