Scientific Research Publishing

Modern Research in Inflammation, 2025, 14(1), 1-19
https://www.scirp.org/journal/mri
ISSN Online: 2169-9690
ISSN Print: 2169-9682

Cutaneous Manifestations of Bone Marrow Edema Syndrome: A Dermatologic-Orthopedic Correlation

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How to cite this paper: Rizzo, D., Rasmussen, J., Stein, M., Severini, C., Tade, Y., Matatov, D., Langelm, D. and Frasier, K. (2025) Cutaneous Manifestations of Bone Marrow Edema Syndrome: A Dermatologic-Orthopedic Correlation. *Modern Research in Inflammation*, **14**, 1-19.
https://doi.org/10.4236/mri.2025.141001

Received: January 3, 2025
Accepted: February 16, 2025
Published: February 19, 2025

Abstract

Bone marrow edema syndrome (BMES), is a rare and self-limiting condition characterized by localized bone pain and transient marrow edema visible on MRI. BMES has been increasingly associated with specific cutaneous manifestations that may hold diagnostic and prognostic significance. Patients with BMES have reported localized erythema, dermal thickening, and induration overlying the affected joints, which are hypothesized to reflect microvascular compromise and inflammatory processes within the bone and adjacent soft tissues. Dermatologic signs are likely linked to regional hyperemia, venous stasis, and cytokine-mediated inflammation, paralleling the pathophysiological mechanisms underlying intraosseous edema. Elevated intraosseous pressure in BMES may disrupt local perfusion, resulting in ischemia-reperfusion injury and subsequent vascular leakage, which manifests in visible cutaneous changes. Pro-inflammatory mediators, such as interleukin-1β and vascular endothelial growth factor (VEGF), central to BMES pathogenesis, may exacerbate endothelial activation, and dermal involvement. Histopathologic studies of affected skin have revealed perivascular lymphocytic infiltration and increased dermal vascularity, further supporting the theory of a shared ischemic and inflammatory pathway between bone and skin. Although MRI remains the gold standard for BMES diagnosis, recognition of these cutaneous manifestations could expedite orthopedic referral and intervention, especially in cases where imaging is delayed or symptoms are ambiguous. Current treatment options, including bisphosphonates, prostacyclin analogs, and offloading

of weight bearing, may benefit from integration with dermatologic strategies to alleviate localized cutaneous symptoms and improve patient comfort. Evaluating the molecular and vascular links between BMES and its cutaneous manifestations provides an opportunity to refine diagnostic protocols and therapeutic approaches, offering a comprehensive understanding of the systemic interplay between dermal and skeletal pathophysiology, and optimizing clinical outcomes for patients affected by BMES.

Keywords

Bone Marrow Edema Syndrome, Cutaneous Manifestations, Microvascular Compromise, MRI Diagnosis, Pro-Inflammatory Mediators, Dermatologic-Orthopedic Correlation

1. Introduction

Bone marrow edema syndrome (BMES) is a rare, self-limiting condition defined by localized bone pain and temporary marrow edema detectable on magnetic resonance imaging (MRI). Because BMES is a relatively rare clinical condition and has been insufficiently documented in the literature, physicians are not adequately aware of the disease, leading to misdiagnosis, mistreatment, extended course of disease, and reduction in patient quality of life [1]. Early recognition and accurate diagnosis of BMES is crucial to prevent unnecessary interventions and ensure appropriate management. BMES was first identified by Curtiss and Kincaid in 1959 as a clinical syndrome, which was marked by pregnant patients presenting with hip pain and reduced bone density on x-ray [1]. Since its initial characterization, BMES has been observed in a broader population, including men and non-pregnant women, with common sites of involvement extending past the hip to include the knees, ankles, and feet.

Over time, BMES has been described using various terms, including *transient osteoporosis*, *transient bone marrow edema, bone marrow edema lesions*, *algodystrophy*, *transient BMES*, *and reversible migratory osteonecrosis* [2]. Among these, *transient osteoporosis* became one of the more frequently used terms. With advancements in MRI, the terminology began to unify, as MRI allowed for more consistent and accurate identification of the condition. In 1988, when BMES was observed on MRI in patients without histologic evidence of osteoporosis following bone marrow biopsy, it was proposed that the term *transient BMES* replace *transient osteoporosis* to better reflect the findings [2]. This shift in terminology marked a step toward distinguishing BMES as a unique identity. However, its relationship to other bone disorders, such as osteonecrosis, has remained a subject of debate. Although BMES is now accepted as a diagnosis with its own specific clinical imaging and features, some authors still endorse that BMES is an abortive form of osteonecrosis [3]. This perspective is most likely due to the overlapping clinical presentation and imaging findings between BMES and early-stage

osteonecrosis, especially the presence of bone marrow edema itself. However, BMES, unlike osteonecrosis, is a self-limiting syndrome that does not typically progress to the destruction of bone long-term, upholding its classification as a distinct, benign condition.

The etiology and pathogenesis of BMES remain incompletely elucidated. BMES is thought to result from either capillary leakage due to local change in the capillary wall from trauma or tumors, or elevated intravascular pressure [4]. Capillary leakage triggers increased interstitial fluid within the bone marrow, perhaps contributing to the development of pain and edema. Elevated intravascular pressure can increase edema through higher blood flow and through impaired venous outflow. There are two types of elevated intravascular pressure associated with bone marrow: hyperemic stems from increased blood flow to the marrow and congestive results from decreased venous clearance of its tissue [4]. These pressure and leakage-related changes contribute to the effects most likely underlying the pain associated with BMES. BMES-related pain likely results from irritation or disruption of sensory nerves within the neurovascular structures of the bone marrow [4]. These neurovascular bundles are essential in supplying innervation and nutrients to the bone marrow, which contribute to bone marrow function. BMES primarily affects the lower extremities, specifically the hips, knees, ankles, and feet, with patients rarely experiencing it in the upper extremities [2]. This preference for the lower extremities may be attributed to the increased weight-bearing demands and higher mechanical loads on these areas, perhaps aggravating vascular and pressure-based changes in the bone marrow.

The history of BMES provides a framework for studying its dermatologic manifestations by highlighting the evolving understanding of the condition. Initially identified by its orthopedic symptoms, such as marrow edema and localized bone pain, early characterizations of the disease centered on specific patient groups, *i.e.*, pregnant women, and specific anatomical sites, *i.e.*, hips. Over time the greater recognition of BMES in diverse populations and its involvement in other joints highlight the complexity and variability of the syndrome. This evolving understanding emphasizes the importance of expanding the clinical perspective to include non-orthopedic symptoms, such as dermatological manifestations, which may have been previously overlooked or underreported in descriptions of the syndrome. By acknowledging this development in clinical understanding, this review aims to address gaps in current medical knowledge, enhance early recognition of atypical presentations, and promote a more comprehensive approach to the diagnosis and management of BMES.

Skin findings, or cutaneous manifestations in systemic conditions, are an important sign of internal disease processes. Many rheumatologic diseases and hematologic diseases often manifest cutaneously, allowing these conditions to be diagnosed earlier and more accurately. There are also orthopedic pathologies that have dermatologic manifestations. Osteomyelitis is a bone infection characterized by inflammation, which can be acute or chronic, and can have dermatologic

manifestations. Although not typically associated with its presentation, osteomyelitis may imitate cellulitis and should be on a differential for a localized skin infection that is unresponsive to initial antibiotic treatment [5]. Carpal tunnel syndrome is a more common condition observed in the general population. In addition to its primary features, carpal tunnel syndrome may occasionally present with cutaneous manifestations, such as sclerodactyly and Raynaud phenomenon of the fingers in the sensory distribution of the median nerve [5]. Cutaneous signs, such as these, are important clues for diagnosis, severity, and progression of the disease. Other cutaneous manifestations observed in carpal tunnel syndrome include nail changes with dystrophic changes and koilonychia, acral osteolysis, and ulcerating lesions and purulent inflammation at the end of digits, sometimes resulting in autoamputation [5]. Recognition of these manifestations by dermatologists can lead to expedited orthopedic surgery referrals to prevent or inhibit the process of autoamputation.

The skin-bone correlations in BMES warrant further investigation, as they may provide valuable diagnostic insights and help differentiate BMES from similar musculoskeletal conditions. BMES is often limited to MRI with the patient's history for confirmation of diagnosis. Investigation of other clinical manifestations of the disease, such as the dermatologic findings, can provide another diagnostic tool for physicians. While BMES primarily affects the bone and its vascular structures, evolving evidence suggests that cutaneous manifestations could play a role in earlier diagnosis and guidance on treatment and management. Understanding these cutaneous manifestations may also strengthen interdisciplinary collaboration between dermatologists and orthopedic surgeons, ultimately enhancing overall patient outcomes. This review aims to elucidate the dermatologic manifestations associated with BMES and explore their implications in diagnosis and management in orthopedic care. Given the overlap in presentation with early osteonecrosis, these dermatologic manifestations may enable earlier and more accurate diagnosis of BMES. Recognition of these manifestations could also allow earlier orthopedic referral and intervention in cases with vague symptoms or limited access to imaging.

2. Pathophysiology of Bone Marrow Edema Syndrome

Currently, the pathogenesis of bone marrow edema syndrome (BMES) remains unknown, with leading postulations centered around thromboembolic events, vascular abnormalities, and insufficient fibrinolysis [2] [4] [6]. While no conclusive etiology has been determined, the pain is believed to originate from increased fluid in the bone marrow interstices, resulting in intraosseous pressure and aggregation of neurovascular bundles within the bone marrow. Variations in the drainage modality of intraosseous capillaries may mediate the increase in the extracellular volume of marrow fluid. Additionally, edema may result from blood congestion due to osseous trauma that can cause capillary damage [7]. Histological assessment reveals osteoid seams within bony trabeculae, as well as novel bone

production and vascular reconstruction with under-mineralized bone [8]. Bone's restorative capacities and its mechanisms of turnover may explain the natural regression of symptoms associated with bone marrow edema syndrome. Further investigation is needed to elucidate the underlying pathophysiology of BMES.

3. Clinical Presentation and Diagnosis of Bone Marrow Edema Syndrome

Bone marrow edema syndrome (BMES) primarily affects the weight-bearing bones of the lower extremities, accounting for up to 98% of cases [9]. The hip is the most commonly affected region, followed by the bones around the knee, ankle, and foot. Proximal joints are typically affected earlier than peripheral ones, which may become involved months later [10]. Furthermore, BMES shows a predilection for young-to-middle-aged adults, particularly males, with an incidence ratio of 3:1 compared to females [11]. A migratory component is observed in approximately 40% - 70% of cases [10] [12]. MRI patterns of bone marrow edema are nonspecific, showing low signal intensity on T1 images and high signal intensity on T2 fat-suppressed sequences, with homogeneous intravenous gadolinium uptake [13]-[15]. While MRI is the current gold standard, diagnosis can often be made with radiographic imaging, reserving MRI for uncertain cases.

Plain radiographs may initially appear normal at symptom onset where the joint space remains intact with no observable subchondral lesions [16]. Bone demineralization and osteopenia may not become evident 3 - 6 weeks later [16]. MRI is superior compared to x-rays as it typically detects diffuse bone marrow edema within 2 days of symptom onset [4] [17]. Clinically, patients present with significant, debilitating pain that limits their activities of daily living and quality of life. Patients with BMES often experience insidious pain and swelling during activity and at rest, findings that can also occur in other conditions [18] [19]. Patients often experience worsening pain over several months, followed by eventual regression and resolution. MRI can help with earlier diagnosis, especially in patients who present with insidious pain in an extremity.

4. Dermatologic Manifestations Associated with Bone Marrow Edema Syndrome

4.1. Overview of Dermatologic Findings

Dermatologic manifestations associated with bone marrow edema syndrome (BMES) remain poorly characterized in the scientific literature. While cutaneous symptoms such as erythema, edema, or discoloration of the overlying skin are not hallmark features of BMES, these manifestations could occur as secondary phenomena related to underlying inflammatory or vascular components [15]. The variability in the etiology of BMES significantly influences the potential for associated skin findings. For example, BMES resulting from trauma may present with clinical findings like ecchymosis. However, BMES secondary to vascular conditions, like sickle cell anemia, might exhibit cutaneous hallmarks of the primary

disease, such as persistent and recurrent leg ulcerations [20] [21]. Currently, no definitive dermatologic markers of BMES have been established, necessitating a high index of suspicion for diagnosis based on a comprehensive clinical history, physical examination, and imaging.

Localized changes in skin temperature overlying areas of BMES have been sporadically documented, though these are neither common nor diagnostic features of the syndrome. Transient erythema and skin changes have been observed in cases undergoing treatments like extracorporeal shock wave therapy (ESWT), highlighting that such manifestations may be secondary to therapeutic interventions rather than the syndrome itself [22]. The etiology of BMES also appears to influence these dermatologic findings. For instance, gout-associated BMES may present with erythema, swelling, and warmth over affected joints, consistent with the inflammatory nature of gout [23]. Similarly, inflammatory or infectious processes involving the joint can result in warmth detectable on physical examination, further emphasizing the role of underlying pathology in shaping dermatologic presentations. Complex regional pain syndrome type I (CRPS-I) represents a condition with overlapping imaging features with BMES, particularly on MRI. The dermatologic associations of CRPS-I are well-documented and include an early "warm stage" characterized by pain, edema, functional limitation, and sensory symptoms [24]. This stage may progress to a "dystrophic phase," with reduction in edema, and ultimately an "atrophic phase," where skin atrophy and contractures become predominant [25]. Although distinct from BMES, these phases highlight the potential for dermatologic changes in conditions that share overlapping pathophysiological processes, underscoring the need for a nuanced approach in evaluating BMES-associated cutaneous findings. The lack of specificity in BMES cutaneous manifestations to other inflammatory conditions, such as gout or CRPS-I, further validates the need for further investigation into differentiating factors for diagnosis. There are currently no clear criteria for differentiating BMES-related dermatologic manifestations from other inflammatory conditions.

4.2. Influence of Pathogenesis on Dermatologic Findings

BMES involves vascular and inflammatory processes that significantly influence its pathophysiology and may extend to dermatologic manifestations. Perfusion abnormalities in BMES, including venous outflow obstruction and intraosseous hypertension, result in ischemia and subsequent angiogenesis. This ischemic environment could theoretically predispose patients to angiogenesis-related skin conditions, such as psoriasis. Interestingly, therapies targeting vascular endothelial growth factor (VEGF), such as Bevacizumab, have been explored in angiogenesis-driven conditions and could represent a future avenue of investigation in BMES-associated skin changes [26]. Inflammation also plays a central role in BMES, with elevated proinflammatory cytokines and chemokines contributing to increased osteoclastic activity and bone erosion [27]. This proinflammatory milieu bears similarities to the pathophysiology of dermatologic conditions, such as

psoriasis and atopic dermatitis, which are also driven by activated T-cell mediators and cytokines [28]. Such overlapping mechanisms provide a potential link between BMES and dermatologic diseases, warranting further investigation.

4.3. Role of Neurogenic and Vascular Mechanisms

The neurological aspects of BMES offer additional insights into its potential dermatologic manifestations. Neurogenic inflammation, mediated by neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP), plays a significant role in localized skin changes. These neuropeptides, released from sensory nerve endings, can induce vasodilation, increased vascular permeability, and subsequent skin changes, including erythema and increased skin temperature [29]. Autonomic nervous system dysfunction may also contribute to cutaneous manifestations, as suggested by reports of dysesthesia and hypoesthesia in the skin overlying affected areas of BMES [30]. Sympathetic nerve fibers, which regulate blood flow and vascular tone in bone marrow, and nociceptive fibers, involved in pain transmission, further underscore the interplay between neurological and vascular mechanisms in BMES-related skin changes [31]. Existing evidence suggests that dermatologic changes, when present, may reflect underlying vascular, inflammatory, or neurological processes associated with BMES. These manifestations are highly variable and context-dependent, emphasizing the importance of a holistic approach to diagnosis that integrates clinical history, imaging findings, and an improved understanding of pathophysiologic mechanisms.

5. Dermatologic Clues as Diagnostic Tools in Bone Marrow Edema Syndrome

5.1. Early Recognition of Dermatological Signs

Dermatologic clues for diagnosing bone marrow edema syndrome (BMES) are not well-documented, as the condition is primarily characterized by bone pain and distinctive MRI findings. However, localized cutaneous changes influenced by vascular, inflammatory, and neurological processes may provide valuable diagnostic insights that merit further investigation. Although rare, localized erythema and edema associated with BMES could stem from neurogenic inflammation and increased vascular permeability. These processes are mediated by neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), which are involved in vasodilation and inflammation [29]. Neurogenic inflammation occurs when nociceptive nerve fibers release neuropeptides, resulting in increased blood flow, vascular permeability, and local inflammatory responses. Bone marrow-derived cells, including mast cells and myeloid cells, play a key role in this process by releasing pro-inflammatory cytokines and chemokines, such as IL-1β, IL-6, TNF-α, and CCL2, which contribute to the inflammatory environment [32]. Similarly, increased skin temperature over the affected area may result from vasodilation and enhanced perfusion driven by the release of these neuropeptides. Sensory changes, such as dysesthesia or hypoesthesia, have also been

reported in BMES, and may reflect autonomic nervous system dysfunction involving small nerve fibers or impaired vascular tone [33]. Additionally, the presence of telangiectasia, though non-specific, may suggest underlying vascular abnormalities associated with BMES pathophysiology [34]. This phenomenon could be linked to the increased angiogenesis observed in bone marrow lesions, characterized by the heightened expression of angiogenic markers, such as CD31 and von Willebrand factor [35]. The resulting fragile new blood vessels are prone to dilation and telangiectasia [35]. While these dermatologic findings are not diagnostic on their own, they offer valuable supplementary clinical clues. When integrated with clinical symptoms and MRI findings, these observations may enhance a comprehensive diagnostic approach for BMES.

Early identification of dermatologic signs and symptoms can expedite the diagnostic process, particularly when MRI is warranted for confirmation. MRI remains the gold standard for BMES diagnosis, as it identifies diffuse, irregular signal hyperintensity on T2-weighted images and decreased signal intensity on T1-weighted images, which are characteristic findings [36]. These MRI findings are crucial for distinguishing BMES from other conditions with similar clinical presentations, such as osteonecrosis, osteomyelitis, or reflex sympathetic dystrophy (RSD). Prompt diagnosis also enables early initiation of conservative management strategies, including non-weight-bearing measures, physical therapy, and analgesic treatment to alleviate symptoms and prevent worsening [37]. Emerging interventions, such as bisphosphonate therapy, iloprost infusions, and extracorporeal shock wave therapy (ESWT) have demonstrated efficacy in reducing bone marrow edema, alleviating pain, and potentially shortening the disease duration [38]. Therefore, recognizing subtle dermatologic changes, even if nonspecific, can be clinically meaningful in guiding timely imaging and management to improve patient outcomes. However, further investigation is needed to determine the specificity of cutaneous manifestations of BMES compared to similar pathologies.

Distinguishing BMES from other orthopedic conditions with overlapping clinical features requires a multidisciplinary approach integrating physical examination, imaging, and dermatologic assessments. While MRI remains the gold standard for diagnosing BMES, physical exam findings can help refine the differential diagnosis. For example, localized erythema and edema, which are indicative of neurogenic inflammation and increased vascular permeability, may also be observed in inflammatory arthritis and infections in addition to BMES [22]. Similarly, increased skin temperature over the affected site, though suggestive of neurogenic inflammation, is a nonspecific finding frequently associated with infectious and systemic inflammatory processes [36]. Dysesthesia or autonomic nervous system symptoms, often linked to BMES, can mimic neuropathic conditions, such as complex regional pain syndrome (CRPS) [30]. Differentiating BMES from osteonecrosis is particularly critical, as osteonecrosis is typically characterized by subchondral bone changes, reduced perfusion, and alterations in mean transit

time on MRI [3]. Despite the overlap in dermatologic and clinical features, certain physical findings can aid in narrowing the diagnosis. Patients with BMES frequently report dysesthesia or hypoesthesia over the skin above the affected bone. Additionally, ipsilateral hyporeflexia at the affected joint, a distinguishing feature of BMES, may result from autonomic nervous system dysfunction [30]. BMES involves increased intraosseous pressure and mechanical stimulation of bone marrow, activating Aδ and C-fiber nociceptors. These nociceptors, which express ion channels and receptors like Piezo2, are sensitive to mechanical stress and contribute to pain signaling. Their activation can lead to referred pain and cutaneous hypersensitivity in the overlying skin, presenting as dysesthesia or hypoesthesia [39]. Conditions like osteonecrosis and infections may share localized pain and skin changes, but these are typically accompanied by more aggressive radiologic findings. In contrast, BMES is self-limiting and characterized on MRI by bone marrow edema without aggressive features [3]. Adopting a holistic diagnostic perspective that considers the patient's overall presentation, alongside key physical, dermatologic, and radiologic findings, is essential for distinguishing BMES from other conditions.

5.2. Case Studies and Clinical Reports

Although dermatologic manifestations may provide supportive evidence for BMES, they are inconsistent and lack sensitivity and specificity, as demonstrated by variable presentations in case reports. For example, one case report noted the absence of erythema or warmth over the affected area, suggesting that dermatologic findings may not always accompany BMES [40]. In contrast, another case described atrophic, discolored, and cool skin with associated allodynia, reflecting neurogenic and vascular dysregulation [41]. Furthermore, a case involving BMES of the femoral head documented systemic paresthesias affecting the hands, feet, and back of the neck, accompanied by generalized pruritus, highlighting the potential for atypical sensory involvement [42]. These discrepancies suggest that dermatologic clues are not pathognomonic for BMES, but can contribute to clinical suspicion when present alongside typical bone pain and imaging findings. Given the heterogeneity of these presentations, clinicians must remain vigilant and consider dermatologic signs as supplementary evidence rather than definitive diagnostic criteria.

Overall, dermatologic findings in BMES, though rare and non-specific, may offer valuable clues for early diagnosis and differentiation from similar conditions. Localized erythema, edema, increased skin temperature, telangiectasia, and sensory changes are suggestive of underlying neurogenic and vascular processes, but lack diagnostic specificity. These findings, when carefully integrated with clinical symptoms and MRI results, can raise clinical suspicion and expedite the diagnostic process, enabling early intervention. Variability in dermatologic presentations across case reports underscores the need for further investigation to elucidate the role of cutaneous findings in BMES. Ultimately, a multidisciplinary approach that

includes physical examination, imaging, and a thorough understanding of associated dermatologic manifestations is essential for the timely diagnosis and effective management of BMES.

6. Interdisciplinary Approach to Bone Marrow Syndrome Management

6.1. Role of Dermatologists in BMES Management

The interdisciplinary approach to managing bone marrow edema syndrome (BMES) underscores the critical role of dermatologists in diagnosing and monitoring the progression of this condition, particularly through the identification of cutaneous markers. BMES is a multifaceted condition primarily diagnosed through MRI, but associated dermatologic signs, such as localized erythema, dermal thickening, and induration over the affected joints, may offer valuable diagnostic clues. These cutaneous manifestations are believed to result from microvascular compromise and inflammatory processes that parallel the intraosseous edema observed in BMES, which can include ischemia-reperfusion injury and vascular leakage [43]. Dermatologists are trained to identify these subtle signs early, potentially expediting orthopedic referrals and interventions when MRI results are inconclusive or delayed.

In particular, dermatologic assessment is beneficial in several scenarios where cutaneous manifestations may indicate disease activity or progression. For example, localized hyperemia and increased vascularity over the affected joints could signal heightened inflammatory responses or worsening ischemic conditions. The observed skin changes, including regional hyperemia and increased vascularity, are thought to be driven by pro-inflammatory cytokines, such as interleukin-1β and vascular endothelial growth factor (VEGF), which also play a role in BMES pathogenesis [44]. Linking the pathophysiology of the skeletal and skin systems calls for the incorporation of dermatologic care for the management of BMES, and further underscores the need to investigate shared ischemic and inflammatory pathways. Similar to cutaneous inflammation, histopathologic examination of affected bone marrow lesions shows fibrosis, lymphocytic infiltrates, and increased vascularization [45]. Continuous dermatologic evaluation can provide insight into systemic disease activity by monitoring disease progression and treatment responses through assessment of changes in skin manifestations over time. Dermatologists can track subtle changes in skin findings, such as reduction in erythema or skin thickness, which could indicate improvement or regression of BMES, and ultimately help orthopedic surgeons gauge the selection or effectiveness of treatment plans. Importantly, for patients with significant cutaneous involvement, dermatologists could offer interventions while orthopedic surgeons assess bone healing. Coordinating clinical care in the outpatient setting between dermatology and orthopedics has limitations, especially in the community setting or with private-practice models. Some barriers to interdisciplinary collaboration include using different electronic health records, different hospitals or outpatient facility

locations of the physicians, not having a dermatologist available in the inpatient setting, and insurance barriers to accessing dermatologists and orthopedic surgeons in an efficient manner.

6.2. Contribution of Orthopedic Surgeons

Orthopedic surgeons play a critical role in managing the bone and joint symptoms of BMES while also addressing any associated cutaneous findings. BMES is characterized by localized bone pain and transient marrow edema, which is best visualized on MRI. Orthopedic surgeons are responsible for interpreting findings, correlating them with clinical symptoms, laboratory workup, and distinguishing BMES from other conditions, such as osteonecrosis or stress fractures [46]. Given the inflammatory and ischemic mechanisms underlying BMES, orthopedic surgeons employ pharmacologic interventions, including nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, and prostacyclin analogs, to reduce inflammation, alleviate bone pain, and promote edema resolution. Studies have shown that bisphosphonates could be used as first-line therapy, as they improve intraosseous circulation and reduce bone resorption, resulting in significant pain relief, faster recovery, and long-term anti-inflammatory effects in BMES [47]. Additionally, prostacyclin analogs have demonstrated efficacy in reducing severe pain, improving functional recovery, and achieving complete regression of bone marrow edema [48]. By improving microvascular perfusion, prostacyclin analogs address both skeletal symptoms and the associated vascular compromise contributing to cutaneous changes in BMES.

Non-pharmacologic strategies, such as physical therapy and activity modification, are integral to conservative BMES management. Orthopedic surgeons may emphasize the importance of offloading the affected joint to reduce mechanical stress, which helps lower intraosseous pressure, and likely reduces further vascular compromise [49]. This involves activity restriction in the acute phase, followed by gradual reintroduction of weight-bearing exercises under guided physical therapy. Dermatologists can educate patients on the importance of moisturizing and protecting the skin from irritation or breakdown, especially when engaging in physical therapy or joint offloading. Online educational tools by dermatologists could help orthopedic surgeons reinforce those recommendations, especially if dermatologists collaborate with orthopedic surgeons. Orthopedic surgeons can reinforce this by explaining how offloading reduces intraosseous pressure and may alleviate both bone pain and associated skin irritation. This shared patient education enhances collaboration between orthopedic surgeons and dermatologists. Structured physical therapy remains a mainstay for symptomatic management, as it improves joint function, strengthens surrounding musculature, and enhances long-term outcomes by reducing recurrence [2] [50]. Orthotics and assistive devices further support joint offloading and pain relief, particularly in weight-bearing bones. Numerous other conservative treatment modalities, such as extracorporeal shock wave therapy, hyperbaric oxygen therapy, electrostimulation, and

pulsed electromagnetic field therapy, have been performed [48]. However, they have not been shown to prevent the disease effectively [48]. Orthopedic surgeons serve an integral role in monitoring disease progression and treatment efficacy through follow-up imaging and clinical assessments, adjusting the therapeutic plans as necessary.

6.3. Collaborative Strategies for Comprehensive Care

Collaboration between orthopedic surgeons and dermatologists is essential to comprehensively manage BMES, especially given the association between skeletal symptoms and cutaneous manifestations. The dermatologic manifestations require further investigation to assess for specificity in BMES compared to other inflammatory pathologies. Skin-directed therapies, including topical corticosteroids, emollients, and anti-inflammatory agents, can alleviate localized skin discomfort and complement systemic treatments, such as bisphosphonates and prostacyclin analogs. While not a common side effect, increased skin dryness and irritation can occur with both bisphosphonates and prostacyclin analogs, and can be carefully managed by dermatologists in concert with orthopedists. Collaborative efforts are foundational, as evidence shows that calcineurin inhibitors, which are commonly used by dermatologists for their anti-inflammatory properties, could contribute to the development of BMES [51]. By addressing both the skeletal and cutaneous symptoms, this interdisciplinary approach ensures improved patient comfort and clinical outcomes. Orthopedic surgeons also benefit from dermatologic monitoring, as changes in skin manifestations can provide insights into disease progression and treatment response [52]. This collaboration enables healthcare providers to refine therapeutic strategies, bridging pharmacologic treatments, physical therapy, and dermatologic care to address the underlying inflammatory and ischemic processes. By managing BMES as a systemic condition with cutaneous and skeletal involvement, orthopedic surgeons and dermatologists can create integrated treatment plans that prioritize both functional recovery and symptom relief.

7. Future Directions

7.1. Research Gaps in Dermatologic Manifestations

Bone marrow edema can be distinguished into three categories known as inflammatory pattern, bone marrow edema syndrome (BMES), osteoarthritis, and secondary to trauma. BMES includes a group of metabolic bone diseases like Transient Regional Osteoporosis and Complex Regional Pain syndrome type 1 [53]. These diseases occur due to inflammatory responses within the body. Therefore, inflammatory symptoms can be used as markers for diagnosis, including cutaneous manifestations. However, there is currently limited documentation of the cutaneous manifestations noticed within patients with BMES. There is no clear explanation for the structural changes that are seen within these patients [54]. This review demonstrates the need for larger cohort studies to understand the different

types of cutaneous manifestations that may arise with BMES. With an improved understanding of BMES symptoms, this may lead to an earlier MRI study and diagnosis. In turn, it may provide treatment sooner to the patient. Additionally, larger cohort studies would create more power. Further studies need to explore the mechanistic pathway leading to the structural changes, as there is no clear etiology of the syndrome [55]. Currently, there are many different options for patient treatment with BMES. However, defining the mechanistic pathway may help physicians assess whether surgical or non-surgical interventions are appropriate.

With BMES typically having inflammatory markers, it may result in other symptoms within the body. This may cause cutaneous symptoms to arise, as there is soft tissue inflammation that is seen that extends to the bone [53]. With soft tissue inflammation, there can be erythema noticed around the area that can be interpreted as a non-invasive diagnostic indicator. Additionally, patients have been observed to have skin discoloration and edema within the affected area [54]. When patients seek evaluation of BMES symptoms, orthopedic surgeons may use MRI to help with their differential diagnosis. It has been seen that there were increased levels of alkaline phosphatase, Type I N-terminal propeptide, and C-terminal cross-linking telopeptide [56]. Biomarkers may be used alongside the cutaneous symptoms to aid in therapeutic management. Therapeutic management currently includes a wide variety of options. Initially, conservative treatment is recommended. Current treatment options include extracorporeal shock wave therapy, pulsed electromagnetic fields, iloprost, and bisphosphonates [55]. By using a combination of treatment options, it may lead to better results for patients. Combination therapy may lead to decreased inflammation and prevent progression of pain they experience. Using an interprofessional approach, through dermatology and orthopedic surgery, may provide a holistic approach to the treatment. For example, dermatologists may use topical steroid creams, which can decrease the soft tissue swelling. Orthopedic surgeons may monitor the patient's pain to see if core decompression is needed, as edema increases pressure leading to the pain that the patient experiences. Overall, an interdisciplinary approach can lead to combination therapy that leads to better control and outcomes for the patient.

7.2. Potential Diagnostic and Therapeutic Innovations

The current understanding of BMES pathophysiology and its dermatologic manifestations is limited by a reliance on case reports and anecdotal evidence rather than robust clinical studies or large cohort analyses. This lack of high-quality evidence poses significant challenges in drawing definitive conclusions about the relationship between BMES and its inflammatory, vascular, and neurological features. While proposed links between BMES pathophysiology and cutaneous manifestations, such as erythema, edema, and skin discoloration, are intriguing, these connections remain largely speculative. For instance, the inflammatory response underlying BMES has been suggested to contribute to soft tissue changes extending

to the skin, but the mechanistic pathways driving these changes remain poorly understood. Larger cohort studies are needed to better characterize the spectrum of cutaneous manifestations and identify common patterns that can aid in diagnosis and management. Future research should focus on exploring the molecular and cellular mechanisms behind BMES-related structural and functional changes, as well as the potential utility of biomarkers in diagnosis and treatment monitoring. By advancing our understanding of these aspects, clinicians may be able to achieve earlier diagnosis through non-invasive markers, improve therapeutic strategies, and optimize the use of interdisciplinary approaches to patient care. Ultimately, bridging these knowledge gaps will not only improve patient outcomes but also provide a foundation for developing targeted treatments for BMES and its associated manifestations.

8. Conclusions

Bone Marrow Edema Syndrome (BMES) is a rare condition with localized bone pain, and increasingly associated cutaneous symptoms. BMES symptoms can present similarly to other pathologies, making diagnosis often challenging. There are no definitive dermatologic manifestations of BMES, but some patients have reported nonspecific symptoms including erythema, edema, warmth, or discoloration of the skin. These symptoms can also be present in other orthopedic conditions, such as gout or CRPS-I, as well as secondary to therapeutic interventions like ESWT. The exact etiology of the cutaneous symptoms of BMES is not clear. VEGF-targeted treatments, pro-inflammatory cytokines in BMES, and increased neuropeptide release from the sympathetic nerve fibers highlight that vascular and neurogenic inflammatory processes may contribute to the localized skin changes in addition to bone marrow edema. Currently, the gold standard for diagnosis is MRI of the affected area with transient marrow edema changes seen. Given that the cutaneous manifestations seen with BMES are nonspecific, the presence of these manifestations in combination with localized bone pain should raise clinical suspicion of BMES, and guide earlier assessments. Recognition of these subtle dermatologic changes can prevent misdiagnosis, extended course of disease, and decreased patient quality of life. There is still limited understanding of BMES pathophysiology and its dermatologic manifestations, which is a limitation of this review, and necessitates further investigation.

Interdisciplinary collaboration between dermatologists and orthopedic surgeons in the management of BMES would maximize patient outcomes. Dermatologists have the training to identify subtle changes in cutaneous presentations that would be helpful in the early identification. Orthopedic surgeons have experience interpreting MRI results, and correlating with clinical symptoms to diagnose BMES, and differentiate it from other conditions that may present similarly. Combined therapeutic modalities from both dermatologists and orthopedic surgeons, could approach the illness more holistically and with decreased adverse effects. Skin directed therapies can alleviate local skin discomfort.

Dermatologic interventions can work synergistically with conservative orthopedic measures, like physical therapy, decreased weight bearing of the affected joint, and systemic medications. Management with a combination of orthopedic surgeons and dermatologists can improve the diagnosis and treatment plans for patients with BMES.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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