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REVIEW ARTICLE

ORAL MANIFESTATIONS OF FAMILIAL MEDITERRANEAN FEVER: A NARRATIVE REVIEW

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ABSTRACT

Background: Familial Mediterranean fever (FMF) is the most common inherited autoinflammatory disorder characterized by recurrent episodes of fever and systemic inflammation caused primarily by pathogenic variants in the *MEFV* gene encoding the pyrin protein. Although FMF predominantly affects serosal membranes, joints, and skin, increasing evidence suggests that chronic inflammatory activation may also influence oral tissues and contribute to a variety of oral manifestations. Recognition of these findings is clinically relevant because oral lesions may represent early or accompanying manifestations of systemic inflammatory activity and may overlap with other inflammatory and autoimmune disorders.

Objective: This narrative review aimed to summarize the current evidence regarding oral manifestations associated with familial Mediterranean fever, including mucosal lesions, periodontal alterations, temporomandibular joint involvement, oral manifestations related to systemic complications, and treatment-associated oral findings.

Methods: A narrative literature review was performed using available publications from major biomedical databases, including PubMed/MEDLINE, Scopus, and Web of Science. Relevant studies describing oral manifestations, inflammatory mechanisms, clinical characteristics, and dental considerations in patients with FMF were analyzed. Due to the limited and heterogeneous nature of available evidence, including case reports, observational studies, and clinical reviews, a narrative synthesis approach was applied.

Results: The available literature indicates that recurrent oral ulcerations, particularly aphthous-like lesions, represent the most frequently reported oral finding in patients with FMF. These lesions may occur independently or during periods of increased inflammatory activity and may create diagnostic challenges due to clinical similarity with Behçet disease and other immune-mediated disorders. Additional reported findings include gingival inflammatory changes, altered periodontal responses, temporomandibular joint symptoms associated with inflammatory arthritis, and oral manifestations related to systemic complications such as AA amyloidosis. Long-term colchicine therapy may influence oral health indirectly through modulation of inflammatory activity; however, specific oral adverse effects in FMF patients remain insufficiently investigated.

Conclusions: Although oral manifestations are not considered primary diagnostic criteria for familial Mediterranean fever, they represent clinically relevant findings that may reflect systemic inflammatory activity and influence patient quality of life. Dentists and oral healthcare professionals should be aware of the potential oral presentations of FMF to facilitate early recognition, appropriate differential diagnosis, and multidisciplinary patient management. Further prospective studies are required to better define the prevalence, clinical significance, and biological mechanisms underlying oral involvement in FMF.

Keywords: Familial Mediterranean fever; FMF; oral manifestations; aphthous ulcers; autoinflammatory disease; MEFV gene; periodontal inflammation; colchicine.

1. INTRODUCTION

Familial Mediterranean fever (FMF) is the most prevalent monogenic autoinflammatory disease and represents a prototypical disorder of innate immune dysregulation. It is characterized by recurrent, self-

limited inflammatory attacks accompanied by fever, serosal inflammation, arthritis, and cutaneous manifestations. The disease predominantly affects populations originating from the Mediterranean basin, including Armenians, Turks, Arabs, etc.; however, with increased migration and improved genetic recognition, FMF has been identified worldwide. Although the clinical spectrum of FMF is primarily associated with systemic manifestations, emerging evidence suggests that chronic inflammatory activation may influence multiple tissues, including oral and maxillofacial structures; however, the extent and clinical significance of oral involvement remain incompletely characterized.[1–3]

Historically, FMF was described as a familial condition characterized by recurrent episodes of fever and abdominal pain, but advances in molecular genetics and immunology have significantly expanded the understanding of its pathogenesis. FMF is currently classified among hereditary autoinflammatory disorders, which are distinguished from autoimmune diseases by predominant involvement of innate immune pathways rather than antigen-specific adaptive immune responses. The central pathological mechanism involves dysregulation of inflammasome-mediated inflammation, resulting in excessive production of pro-inflammatory cytokines, particularly interleukin-1β (IL-1β), and uncontrolled activation of neutrophil-dependent inflammatory pathways. [4,5]

The genetic basis of FMF is strongly associated with pathogenic variants in the MEFV gene, located on chromosome 16p13.3. The MEFV gene encodes pyrin, a 781-amino-acid protein expressed mainly in innate immune cells, particularly neutrophils, monocytes, and macrophages. Pyrin functions as a critical regulator of inflammatory signaling by controlling assembly and activation of the pyrin inflammasome. Under physiological conditions, pyrin participates in mechanisms that limit inappropriate inflammatory activation. However, disease-associated mutations may impair this regulatory function, resulting in abnormal inflammasome activation and excessive inflammatory responses. [6,7]

More than 300 variants of the MEFV gene have been described; however, only a subset has been clearly associated with FMF susceptibility and disease severity. The most frequently reported pathogenic variants include M694V, M680I, M694I, and V726A, which are primarily located within exon 10 encoding the B30.2/SPRY domain of pyrin. The M694V variant is considered one of the most clinically significant mutations and has been associated with earlier disease onset, more severe inflammatory attacks, and increased risk of AA amyloidosis. However, genotype–phenotype correlations remain complex, as clinical expression is influenced by additional genetic modifiers, environmental factors, epigenetic mechanisms, and variations in inflammatory regulation.[8–10]

The pathogenesis of FMF involves abnormal regulation of the inflammasome pathway, a molecular platform responsible for activation of inflammatory caspases and maturation of IL-1β. In healthy individuals, pyrin activation is tightly controlled through phosphorylation-dependent mechanisms involving regulatory proteins such as 14-3-3. Mutations affecting pyrin function reduce this inhibitory regulation and promote spontaneous inflammasome assembly. The resulting activation of caspase-1 leads to increased conversion of pro-IL-1β into biologically active IL-1β, which stimulates recruitment and activation of neutrophils and amplifies inflammatory responses. [11,12]

IL-1β represents a central mediator in FMF pathogenesis and contributes to many clinical manifestations of the disease. Increased IL-1 signaling promotes endothelial activation, leukocyte recruitment, vascular permeability, and tissue inflammation. These mechanisms explain the episodic inflammatory attacks affecting serosal membranes, synovial tissues, and skin. Furthermore, persistent subclinical inflammation between attacks may contribute to long-term complications, particularly AA amyloid deposition resulting from chronic elevation of serum amyloid A protein. [13,14]

The clinical phenotype of FMF is highly variable. Typical attacks usually develop during childhood or adolescence and are characterized by episodes of fever lasting 12–72 hours, accompanied by sterile inflammation of the peritoneum, pleura, or synovial membranes. Abdominal attacks resembling acute surgical conditions are among the most common manifestations, while recurrent monoarthritis and erysipelas-like erythema represent other characteristic features. The severity and frequency of attacks vary considerably between patients, even among individuals carrying identical genetic variants, emphasizing the contribution of additional modifying factors. [1,3,15]

The oral cavity has increasingly been recognized as a potential site influenced by systemic inflammatory disorders. Oral tissues represent an immunologically active environment where epithelial barriers, resident immune cells, microbiota, and connective tissues continuously interact. Since FMF is characterized by excessive innate immune activation and neutrophil-driven inflammation, theoretical mechanisms exist through which systemic inflammatory dysregulation may

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influence oral mucosal integrity, periodontal tissues, and healing responses. However, direct clinical evidence linking FMF with specific oral changes remains limited. [16,17]

Among reported oral findings in patients with FMF, recurrent oral ulcerations represent the most frequently described manifestation. These lesions may resemble recurrent aphthous stomatitis and may create diagnostic challenges, particularly because oral aphthous lesions are also common in Behçet disease, another inflammatory disorder prevalent in Mediterranean populations. Differentiating FMF-associated oral findings from Behçet-related manifestations is clinically important, as the two conditions differ in systemic involvement, diagnostic criteria, and therapeutic strategies.[18–20]

The relationship between FMF and periodontal tissues remains an emerging area of investigation. Periodontal tissues are highly responsive to systemic inflammatory mediators, and increased circulating levels of IL-1β, tumor necrosis factor-α (TNF-α), and other cytokines may influence periodontal immune responses. Although definitive evidence establishing FMF as an independent risk factor for periodontal disease is lacking, the biological plausibility of interaction between FMF-associated inflammation and periodontal homeostasis has stimulated further research.[21,22]

Another important aspect of FMF relevant to oral health is the development of systemic complications. Chronic uncontrolled inflammation may lead to AA amyloidosis, which can occasionally involve oral and maxillofacial tissues. Amyloid deposition may result in soft tissue enlargement, tongue involvement, altered mucosal characteristics, and functional disturbances. Although these findings are uncommon, they represent clinically relevant manifestations requiring recognition. [23]

The management of FMF has been revolutionized by colchicine therapy, which remains the cornerstone of disease prevention. Colchicine reduces inflammatory attacks and prevents amyloid deposition by inhibiting microtubule polymerization and neutrophil-mediated inflammatory activity. More recently, biologic therapies targeting IL-1 pathways, including anakinra and canakinumab, have provided therapeutic options for patients with colchicine-resistant or colchicine-intolerant disease. [24–26]

From a dental perspective, awareness of FMF-associated oral findings is important because oral lesions may accompany systemic inflammatory activity or complicate differential diagnosis with other immune-mediated conditions. Dentists and oral healthcare professionals may encounter patients presenting with recurrent unexplained oral ulcers, inflammatory oral changes, or unusual healing patterns and should consider systemic inflammatory disorders within the diagnostic process when appropriate.[18,27]

Despite increasing knowledge regarding the molecular mechanisms of FMF, oral findings remain insufficiently characterized. Current evidence is limited by the predominance of case reports, small clinical series, and heterogeneous diagnostic approaches. The prevalence, pathophysiological mechanisms, and clinical significance of oral involvement in FMF remain incompletely defined. [18,27]

This narrative review aims to provide a comprehensive overview of reported oral findings associated with familial Mediterranean fever, integrating current knowledge regarding genetic mechanisms, immunopathogenesis, clinical presentation, diagnostic considerations, and future perspectives. A better understanding of these findings may contribute to earlier recognition of systemic disease, improved interdisciplinary collaboration, and more comprehensive patient management.

2.MATERIALS AND METHODS

2.1Literature Search Strategy

A narrative literature review was conducted to evaluate the available scientific evidence regarding reported oral findings associated with familial Mediterranean fever (FMF), with particular emphasis on clinical characteristics, genetic background, molecular mechanisms, inflammatory pathways, and implications for oral healthcare. The methodology was designed to provide a comprehensive interpretation of the available literature while considering the heterogeneous and predominantly descriptive nature of evidence related to oral involvement in this rare autoinflammatory disorder.

A structured literature search was performed in the electronic databases PubMed/MEDLINE, Scopus, and Web of Science. Publications available from database inception until 2026 were considered. The search strategy was developed using a combination of controlled vocabulary terms (including MeSH terms where applicable) and free-text keywords related to familial Mediterranean fever, genetic mechanisms, inflammation, and oral findings.

The following search terms and their combinations were used:

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"familial Mediterranean fever",
"FMF",
"MEFV gene",
"MEFV mutation",
"pyrin",
"pyrin inflammasome",
"autoinflammatory disease",
"innate immunity",
"interleukin-1β",
"IL-1β",
"oral manifestations",
"oral findings",
"oral involvement",
"oral ulceration",
"aphthous ulcers",
"recurrent oral ulcers",
"periodontal inflammation",
"oral mucosa",
"temporomandibular joint",
"colchicine therapy".

Boolean operators (AND, OR) were applied to combine search terms and improve identification of relevant publications. Additional studies were identified through manual screening of reference lists from relevant articles to ensure inclusion of important publications not retrieved through the primary database search.

2.2 Study Selection and Data Synthesis

The initial literature search identified 73 potentially relevant publications from the selected electronic databases. Retrieved records were evaluated according to their relevance to the objectives of the present narrative review. The selection process included assessment of article titles, abstracts, and, when necessary, full-text evaluation to determine whether publications provided clinically or biologically meaningful information regarding FMF and its reported oral findings.

Publications were considered eligible when they addressed one or more of the following aspects: genetic mechanisms associated with FMF, particularly MEFV gene variants and pyrin-mediated inflammatory regulation; molecular mechanisms involved in inflammasome activation and IL-1β-mediated inflammation; clinical characteristics of FMF; reported oral and maxillofacial findings; differential diagnostic considerations involving oral lesions; systemic complications with possible oral implications; and therapeutic approaches relevant to disease control.

Studies were excluded when they lacked direct relevance to FMF, did not provide sufficient information regarding disease mechanisms or oral findings, represented duplicate publications, or focused exclusively on unrelated autoimmune or autoinflammatory disorders. Publications without accessible full-text information or without clinically meaningful data were also excluded.

Following qualitative assessment of the available literature, 31 articles were selected for the final narrative synthesis. The included publications represented a heterogeneous range of evidence, including clinical studies, case reports, observational investigations, molecular genetic studies, and review articles. Due to the limited number of studies specifically addressing oral findings in FMF and the substantial variability in study designs, patient populations, and reported outcomes, quantitative statistical analysis was not performed.

The extracted information was analyzed using a descriptive narrative approach. The available evidence was organized into the following major thematic domains:

- genetic basis and molecular mechanisms of familial Mediterranean fever;
- role of MEFV mutations and pyrin inflammasome activation;
- inflammatory pathways contributing to systemic disease manifestations;
- reported oral and maxillofacial findings;
- possible mechanisms linking systemic inflammation with oral tissue responses;
- differential diagnosis of oral lesions associated with FMF;
- clinical considerations for dental practitioners and multidisciplinary management.

2.3 Eligibility Criteria

Inclusion Criteria

Articles were included if they met the following criteria:

- studies involving patients with clinically or genetically confirmed familial Mediterranean fever;
- publications describing reported oral findings or oral-related clinical observations in FMF patients;
- studies investigating the genetic and molecular basis of FMF, including MEFV gene variants and inflammatory mechanisms;
- publications addressing clinical characteristics, diagnosis, treatment, or systemic complications relevant to oral healthcare;
- peer-reviewed articles published in English;
- clinical studies, observational studies, case reports, molecular investigations, and relevant review articles.

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Exclusion Criteria

Articles were excluded if they:

• focused on inflammatory diseases unrelated to FMF;
• investigated general oral ulcerative disorders without an association with FMF;
• lacked information regarding clinical characteristics, genetic mechanisms, or inflammatory pathways relevant to FMF;
• were conference abstracts, unpublished materials, or non-peer-reviewed sources;
• represented duplicated or overlapping reports.

2.4 Data Extraction and Analysis

Relevant information from the included publications was extracted and organized according to predefined categories. Extracted variables included:

• first author and year of publication;
• country and population characteristics;
• study design;
• genetic findings, including reported MEFV mutations;
• molecular mechanisms and inflammatory pathways investigated;
• reported oral findings;
• associated systemic manifestations;
• treatment approaches and potential clinical implications.

Because the available evidence demonstrated substantial heterogeneity in study methodology and outcome reporting, data were synthesized qualitatively rather than quantitatively. The narrative synthesis focused on identifying recurring patterns, clinically relevant observations, possible biological mechanisms, and current limitations in understanding oral involvement in FMF.

2.5 Methodological Considerations

This review was conducted as a narrative review due to the rarity of reported oral findings associated with FMF and the predominance of descriptive evidence. Unlike systematic reviews designed to provide quantitative estimates or evaluate comparative treatment effects, narrative reviews allow integration of diverse evidence sources, including clinical observations, genetic investigations, and mechanistic studies. The selected methodology enabled a broader interpretation of the relationship between FMF-related inflammatory dysregulation and oral health while identifying areas requiring further investigation. Future prospective studies using standardized oral examination protocols, inflammatory biomarker assessment, and genetically characterized FMF cohorts are necessary to clarify the prevalence, clinical significance, and biological mechanisms underlying oral findings in patients with familial Mediterranean fever.

3 RESULTS

3.1 Overview of the Included Literature

The initial literature search identified 73 potentially relevant publications addressing different aspects of familial Mediterranean fever (FMF), including genetic mechanisms, inflammatory pathways, clinical characteristics, systemic complications, and possible oral involvement. All retrieved records were assessed according to their relevance to the objectives of the present narrative review. Following evaluation of titles, abstracts, and available full-text publications, studies lacking clinically or biologically relevant information regarding FMF or its potential oral manifestations were excluded.

After qualitative assessment of the available evidence, 31 articles were included in the final narrative synthesis. The included publications represented a heterogeneous body of evidence comprising clinical studies, case reports, observational investigations, molecular genetic studies, and review articles. The majority of available literature focused on the genetic basis, immunopathogenesis, and systemic manifestations of FMF, whereas a smaller proportion specifically addressed oral and maxillofacial findings.

The available evidence indicates that oral manifestations are not established diagnostic criteria or classical features of FMF. However, several reports have described oral findings occurring in patients with FMF, suggesting that oral involvement may represent an additional clinical observation associated with systemic inflammatory activity. Among the reported oral findings, recurrent oral ulcerations and aphthous-like lesions were the most frequently described. Other less consistently reported manifestations included inflammatory mucosal changes, periodontal alterations, temporomandibular joint symptoms, and oral manifestations associated with systemic complications such as AA amyloidosis. [18,19,21,23]

The reviewed literature also highlighted the complexity of genotype–phenotype relationships in FMF. Although specific *MEFV* variants, particularly exon 10 mutations such as M694V, have been associated with increased disease severity, earlier onset, and higher inflammatory burden, clinical expression remains influenced by

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multiple genetic, environmental, and immunological factors. The main genetic and immunological mechanisms associated with FMF pathogenesis are summarized in Table 1. Whether these factors directly influence the development or severity of oral manifestations remains unclear.[3,8–10]

Table 1. General Characteristics of Included Publications (n = 31)

Characteristic	Findings
Initial records identified	73
Articles included in final narrative synthesis	31
Publication types	Clinical studies, case reports, observational studies, molecular genetic studies, review articles
Main investigated topics	Genetic mechanisms, inflammatory pathways, oral manifestations, systemic complications, treatment considerations
Disease investigated	Familial Mediterranean fever (FMF)
Main genetic focus	MEFV gene variants and pyrin protein dysfunction
Main inflammatory mechanism	Pyrin inflammasome activation and IL-1β-mediated inflammation
Most frequently reported oral findings	Recurrent oral ulcerations, aphthous-like lesions, mucosal inflammatory changes
Overall evidence characteristics	Heterogeneous, predominantly descriptive clinical evidence

3.2 Genetic and Molecular Characteristics of Familial Mediterranean Fever

The included literature consistently identified FMF as a hereditary autoinflammatory disorder primarily associated with pathogenic variants in the MEFV gene located on chromosome 16p13.3. The MEFV gene encodes pyrin, an intracellular protein that plays a central role in regulating innate immune responses through modulation of inflammasome activation. [6,7]

The reviewed studies demonstrated that pathogenic alterations affecting pyrin function may result in dysregulated activation of the pyrin inflammasome, leading to increased caspase-1 activity and enhanced processing of pro-interleukin-1β (pro-IL-1β) into biologicallyctive IL-1β. This inflammatory cascade promotes neutrophil recruitment and contributes to the recurrent inflammatory episodes characteristic of FMF.[1,12,28,29]

Among the reported MEFV variants, M694V, M680I, M694I, and V726A are among the most frequently described pathogenic mutations. Several studies have associated the M694V variant with a more severe clinical phenotype, earlier disease onset, increased frequency of inflammatory attacks, and a higher risk of AA amyloidosis. Nevertheless, genotype alone does not completely determine clinical expression, and disease severity is influenced by additional modifying genetic and environmental factors. [3,8–10]

The relevance of FMF-related inflammatory mechanisms to oral tissues remains hypothetical but biologically plausible. IL-1β signaling and neutrophil-mediated inflammatory responses, which play central roles in FMF pathogenesis, are also involved in mucosal immune regulation, periodontal inflammatory processes, and tissue repair mechanisms. However, direct evidence linking specific MEFV mutations with oral manifestations remains insufficient. [13,14,16]

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The main genetic and immunological characteristics reported in patients with FMF are summarized in Table 2.

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Table 2. Genetic and Immunological Findings Reported in Included Studies

Parameter	Findings
Disease category	Monogenic autoinflammatory disorder
Main genetic alteration	Pathogenic variants of the MEFV gene
Chromosomal location	16p13.3
Encoded protein	Pyrin
Primary molecular abnormality	Dysregulated pyrin inflammasome activation
Major cytokine involved	Interleukin-1β (IL-1β)
Main inflammatory cells involved	Neutrophils, monocytes, and macrophages
Frequently reported mutations	M694V, M680I, M694I, V726A
Genotype–phenotype association	M694V is frequently associated with increased disease severity, earlier onset, and higher inflammatory burden
Major systemic complication	AA amyloidosis
Clinical implication	Variable genotype–phenotype expression influenced by genetic, environmental, and immunological modifiers

The relevance of FMF-related inflammatory mechanisms to oral tissues remains hypothetical but biologically plausible. IL-1β signaling and neutrophil-mediated inflammatory responses, which play central roles in FMF pathogenesis, are also involved in mucosal immune regulation, periodontal inflammatory processes, and tissue repair mechanisms. However, direct evidence linking specific *MEFV* mutations with oral manifestations remains insufficient. [13,14,16]

3.3 Oral Manifestations Associated with Familial Mediterranean Fever

The reviewed literature indicates that oral manifestations have been reported in patients with familial Mediterranean fever (FMF); however, compared with the well-established systemic features of the disease, oral involvement remains insufficiently characterized. Available evidence is derived mainly from clinical observations, case reports, and limited observational studies, making accurate estimation of prevalence and determination of clinical significance challenging. Among the reported oral findings, recurrent oral ulcerations and aphthous-like lesions represent the most frequently described manifestations. [18,19]

Reported oral ulcerations were generally described as painful, recurrent lesions resembling recurrent aphthous stomatitis and involving predominantly non-keratinized mucosal surfaces, including the labial mucosa, buccal mucosa, tongue, and soft palate. In some reports, oral lesions appeared during periods of increased inflammatory activity; however, a consistent association between the presence of oral ulcers and the severity or frequency of systemic FMF attacks has not been established. [18,19]

A major diagnostic consideration is the clinical similarity between FMF-associated oral ulcers and oral manifestations observed in Behçet disease. This overlap is particularly important in populations with a high prevalence of FMF, including Mediterranean populations. Therefore, recurrent oral ulcerations in patients with suspected FMF should not be interpreted as an isolated diagnostic finding but should be evaluated together with systemic manifestations, family history, genetic findings, and other clinical criteria. [19,20]

Beyond mucosal lesions, limited reports have described possible periodontal and maxillofacial involvement in patients with FMF. Although periodontal disease is not recognized as a primary manifestation of FMF, systemic inflammatory activation may theoretically influence periodontal immune responses through shared inflammatory pathways involving IL-1β, TNF-α, and neutrophil-mediated mechanisms. Nevertheless, current evidence remains insufficient to establish FMF as an independent risk factor for periodontal disease. [16,17,21,22]

The main oral manifestations reported in FMF patients and their proposed biological mechanisms are summarized in Table 3.

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Table 3. Oral Manifestations Reported in Patients with FMF

Oral manifestation	Clinical characteristics	Possible pathogenic mechanism
Recurrent oral ulcerations	Painful aphthous-like lesions with episodic recurrence, mainly affecting non-keratinized mucosal surfaces	IL-1β-mediated inflammatory activation and neutrophil-mediated immune responses [18,19]
Oral mucosal inflammation	Erythema, mucosal sensitivity, and inflammatory changes	Systemic inflammatory activation associated with FMF episodes [18]
Aphthous-like lesions	Recurrent ulcerative lesions involving labial mucosa, buccal mucosa, tongue, and soft palate	Altered mucosal immune regulation and inflammatory susceptibility [18–20]
Gingival inflammatory changes	Increased gingival inflammatory response and possible enhanced susceptibility to inflammation	Cytokine-mediated immune dysregulation involving IL-1β and TNF-α pathways [13,14]
Periodontal alterations	Limited clinical observations suggesting possible inflammatory periodontal changes	Interaction between systemic inflammatory pathways and periodontal immune responses [16,17,21,22]
Temporomandibular symptoms	Rare inflammatory joint manifestations associated with FMF-related arthritis	FMF-associated inflammatory arthritis affecting the temporomandibular joint region [1,15]
Amyloidosis-related oral changes	Possible soft tissue enlargement or altered tissue consistency in advanced disease	AA amyloid deposition associated with chronic uncontrolled inflammation [23]

Summary of oral manifestations reported in patients with familial Mediterranean fever (FMF), including clinical characteristics and proposed inflammatory mechanisms. Current evidence suggests that recurrent oral ulcerations are the most frequently described oral finding; however, the prevalence, pathogenesis, and direct relationship with *MEFV* mutations or systemic disease activity remain insufficiently established.

3.4 Recurrent Oral Ulcerations and Diagnostic Considerations

Recurrent oral ulcerations represent the most consistently reported oral finding among patients with FMF. Although these lesions are not specific for FMF, their presence in individuals with recurrent fever episodes, serositis, arthritis, or a positive family history may provide additional clinical information supporting evaluation for an underlying autoinflammatory disorder. [18,19]

The reviewed evidence emphasizes the importance of distinguishing FMF-associated oral lesions from other inflammatory and immune-mediated conditions, particularly Behçet disease. Both disorders may present with recurrent oral ulcerations; however, their underlying pathogenic mechanisms and associated systemic manifestations differ substantially. [20]
In FMF, oral manifestations are considered potentially related to dysregulated innate immune activation and IL-1β-driven inflammatory pathways. In contrast, Behçet disease represents a complex inflammatory vasculitic disorder involving both innate and adaptive immune mechanisms, with oral ulcerations forming one of its major diagnostic features.

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Therefore, differential diagnosis requires comprehensive assessment of clinical presentation, genetic background, systemic manifestations, and laboratory findings rather than evaluation of oral lesions alone.[11,12,20]

The main clinical differences between FMF-associated oral ulcerations and other ulcerative disorders are summarized in Table 4.

Table 4. Clinical differences between FMF-associated oral ulcerations and other ulcerative disorder

Feature	FMF	Behçet Disease	Recurrent Aphthous Stomatitis
Main mechanism	Autoinflammatory process mediated predominantly by IL-1β and innate immune dysregulation [11,12]	Systemic inflammatory vasculitis involving innate and adaptive immune pathways [20]	Localized mucosal immune reaction with multifactorial etiology [27]
Genetic association	Pathogenic MEFV variants, particularly exon 10 mutations [6–10]	Association with HLA-B51 and other immune-related genetic factors [20]	Multifactorial genetic susceptibility [27]
Oral ulcers	Reported with variable frequency; usually aphthous-like and recurrent [18,19]	Frequent, recurrent, and often a major clinical manifestation [20]	Common recurrent oral ulcerations without systemic disease [27]
Typical systemic findings	Recurrent fever attacks, serositis, arthritis, and inflammatory episodes [1,15]	Ocular involvement, genital ulcers, vascular manifestations, and systemic inflammation [20]	Usually absent or limited to oral mucosal involvement [27]
Diagnostic role of oral lesions	Supportive clinical finding; not considered a diagnostic criterion for FMF [18,19]	Major diagnostic component and characteristic clinical feature [20]	Represents the primary clinical manifestation [27]

Comparison of recurrent oral ulcerative manifestations observed in familial Mediterranean fever (FMF), Behçet disease, and recurrent aphthous stomatitis. The table highlights differences in underlying inflammatory mechanisms, genetic associations, systemic manifestations, and the diagnostic significance of oral lesions. Although oral ulcerations may occur in FMF, they lack specificity and should be interpreted within the broader clinical and genetic context.

3.5 Periodontal and Maxillofacial Findings

The relationship between FMF and periodontal tissues remains an emerging field with limited available evidence. Theoretically, chronic inflammatory activation associated with FMF may influence periodontal homeostasis through shared inflammatory mediators, including IL-1β, TNF-α, and other cytokines involved in immune regulation, tissue destruction, and repair processes. [16,17,21,22]

However, current evidence does not support considering periodontal disease as a direct manifestation of FMF. Reported periodontal alterations may reflect increased inflammatory susceptibility in genetically predisposed individuals rather than a specific FMF-associated periodontal phenotype. Future investigations involving genetically confirmed FMF cohorts, comprehensive periodontal examinations, and standardized inflammatory assessments are required to clarify this potential association. [21,22]

Temporomandibular joint involvement has been rarely described in patients with FMF. When present, it may represent part of the broader musculoskeletal inflammatory manifestations of the disease rather than

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a specific oral complication. Clinical findings may include joint pain, restricted mandibular movement, and symptoms associated with inflammatory arthritis. [1,15]

3.6 Treatment-Related Oral Considerations

The reviewed literature confirms colchicine as the cornerstone therapy for FMF, with established efficacy in reducing inflammatory attacks and preventing AA amyloidosis. Colchicine acts primarily through inhibition of microtubule polymerization and suppression of neutrophil-mediated inflammatory activity. However, its specific effects on FMF-associated oral manifestations have not been systematically investigated. [24]

Patients with colchicine-resistant or colchicine-intolerant FMF may receive targeted biological therapies, particularly IL-1 inhibitors such as anakinra and canakinumab. These agents effectively reduce systemic inflammatory activity; however, their influence on oral manifestations, mucosal lesions, and periodontal inflammatory responses remains insufficiently studied. [25–27]

Potential therapeutic approaches and their possible oral implications are summarized in Table 5.

Table 5. Therapeutic Approaches in FMF and Potential Oral Implications

Treatment	Mechanism of action	Possible oral relevance
Colchicine	Inhibition of microtubule polymerization and suppression of neutrophil-mediated inflammatory activity	Reduction of systemic inflammatory activity and attack frequency; possible indirect improvement of inflammation-associated oral manifestations [24]
Anakinra	IL-1 receptor blockade leading to inhibition of IL-1-mediated inflammatory signaling	Potential reduction of IL-1-driven inflammatory responses affecting systemic and possibly oral tissues [25,27]
Canakinumab	Selective neutralization of IL-1β	Suppression of systemic inflammatory activation; potential influence on inflammation-related oral manifestations requires further investigation [26,27]
Dental supportive management	Symptomatic oral care, preventive dental therapy, and management of oral discomfort	Improvement of oral health status, patient comfort, and quality of life; supportive role in patients with recurrent oral lesions

Therapeutic strategies used in FMF and their potential implications for oral health. While colchicine and IL-1-targeted biological therapies effectively control systemic inflammation, their direct effects on FMF-associated oral manifestations remain insufficiently characterized. Supportive dental management remains important for maintaining oral health and improving patient quality of life.

3.7 Summary of Main Findings

The synthesis of available evidence indicates that oral findings may represent an underrecognized aspect of FMF; however, their role within the overall disease phenotype remains incompletely defined. Oral manifestations are not included among the established diagnostic criteria of FMF, and current evidence is insufficient to determine their prevalence or prognostic significance. [18,19]

Among the reported oral findings, recurrent oral ulcerations and aphthous-like lesions represent the most frequently described manifestations. These findings may occur in association with systemic inflammatory activity, although a direct causal relationship has not been conclusively demonstrated.

The available literature suggests that potential oral involvement may be biologically plausible due to the central role of pyrin inflammasome dysregulation, IL-1β signaling, and neutrophil-mediated inflammation in

FMF pathogenesis. Nevertheless, the limited number of dedicated oral studies and the predominance of descriptive evidence prevent definitive conclusions regarding mechanisms, frequency, and clinical relevance. [11–14,18,21,22]

Future prospective investigations involving standardized oral examinations, inflammatory biomarker analysis, and genetically characterized FMF cohorts are required to clarify whether oral manifestations represent independent clinical features, indicators of systemic inflammatory activity, or secondary consequences of chronic inflammation. The figure 1 summarizes the potential oral manifestations reported in FMF, including recurrent aphthous-like ulcerations, possible periodontal inflammatory changes, temporomandibular joint involvement, treatment-related considerations, and oral implications of systemic complications. The central panel illustrates FMF as a monogenic autoinflammatory disorder driven by *MEFV* mutations, pyrin inflammasome dysregulation, IL-1β activation, and systemic inflammatory responses. Current evidence suggests biological plausibility of oral involvement; however, the frequency, mechanisms, and clinical significance of oral manifestations remain insufficiently established.

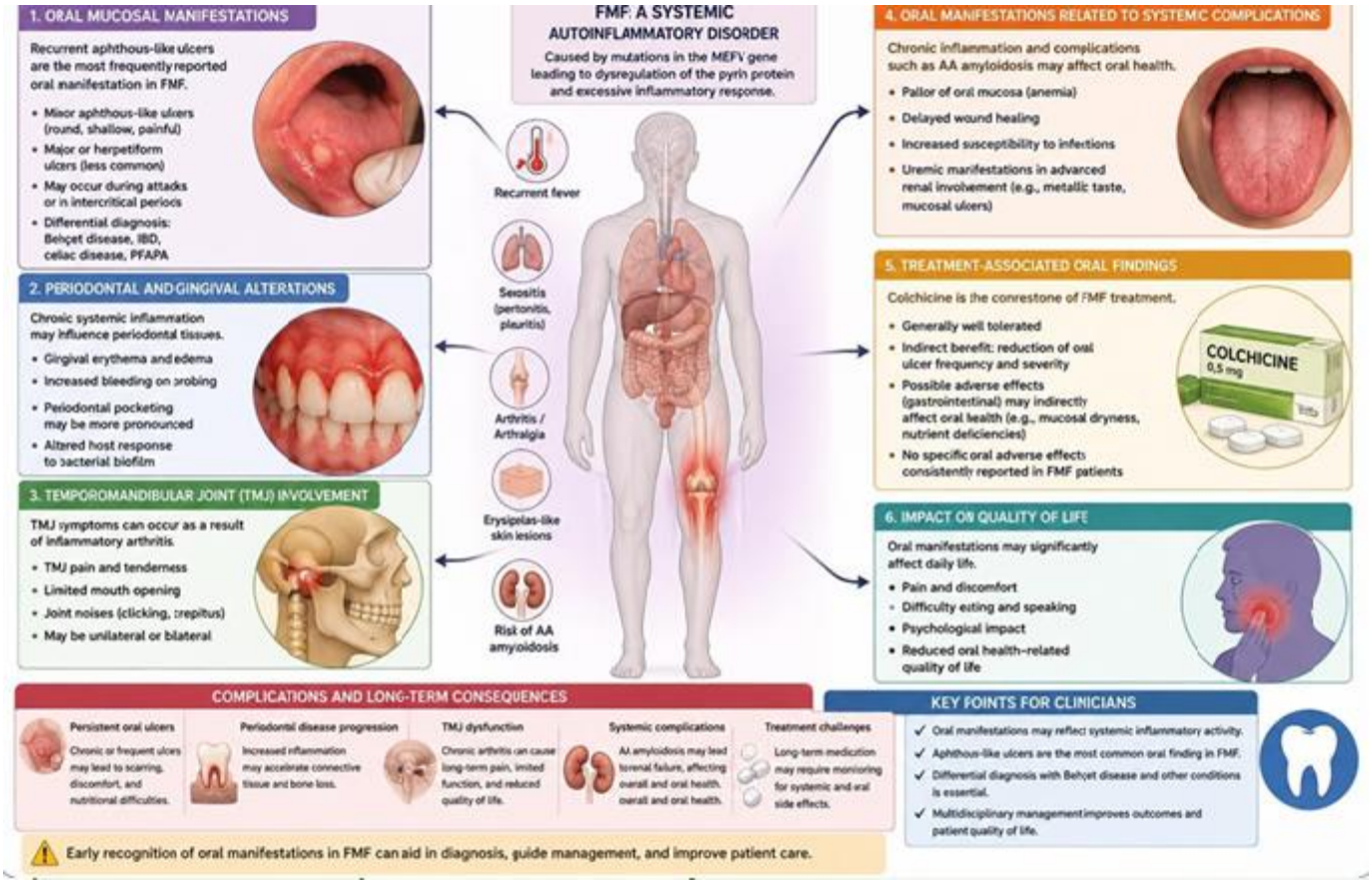

Figure 1. Oral manifestations and complications associated with FMF

4 DISCUSSION

The present narrative review synthesized the available evidence regarding oral manifestations associated with FMF, with particular emphasis on the relationship between genetic abnormalities, innate immune dysregulation, and potential oral and maxillofacial involvement. Although FMF is primarily recognized as a systemic autoinflammatory disorder characterized by recurrent fever episodes, serosal inflammation, arthritis, and the risk of AA amyloidosis, the reviewed literature indicates that oral manifestations may represent an additional, although incompletely defined, component of the disease spectrum. The current

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evidence remains limited; however, the reported findings suggest that oral involvement may reflect the broader inflammatory phenotype of FMF rather than a distinct primary oral manifestation of the disease.[1–5,18,19] The biological plausibility of oral involvement in FMF is supported by the central role of pyrin inflammasome dysregulation and excessive IL-1β-mediated inflammation in disease pathogenesis. Pathogenic variants of the MEFV gene result in impaired regulation of pyrin activity, leading to uncontrolled inflammasome activation, increased caspase-1 activity, and enhanced production of IL-1β. This inflammatory pathway promotes neutrophil recruitment and persistent activation of innate immune responses. Because oral mucosal tissues and periodontal structures are continuously influenced by immune-mediated inflammatory processes, systemic abnormalities in innate immunity may theoretically contribute to altered oral tissue responses in genetically susceptible individuals. However, the currently available clinical evidence does not allow definitive conclusions regarding the extent or clinical importance of this association. Among the oral manifestations reported in FMF patients, recurrent oral ulcerations represent the most frequently described finding. These lesions are generally characterized as painful, aphthous-like ulcers affecting non-keratinized mucosal surfaces. Nevertheless, their prevalence, recurrence pattern, and relationship with systemic inflammatory attacks remain insufficiently established. Unlike Behçet disease, in which recurrent oral ulcerations represent a major diagnostic component, oral ulcers are not included among the diagnostic criteria for FMF. Therefore, their presence should be interpreted as a possible supportive clinical feature rather than a specific diagnostic marker. [18,19] The differential diagnosis between FMF-associated oral ulcerations and Behçet disease represents an important clinical challenge, particularly in Mediterranean populations where both conditions are relatively prevalent. Although both disorders may present with recurrent oral lesions, their immunological mechanisms differ considerably. FMF is primarily characterized by dysregulated innate immunity involving pyrin inflammasome activation and IL-1β overproduction, whereas Behçet disease involves a complex inflammatory process with vasculitic features and interaction between innate and adaptive immune pathways. Consequently, evaluation of recurrent oral ulcers in suspected FMF patients should include comprehensive assessment of systemic manifestations, family history, genetic findings, and other clinical characteristics rather than relying solely on oral findings. [11,12,20] The relationship between FMF and periodontal health remains one of the least explored areas. The available literature suggests a possible interaction between systemic inflammatory activity and periodontal immune responses, mainly because several inflammatory mediators involved in FMF, including IL-1β and TNF-α, also participate in periodontal tissue inflammation and destruction. However, current evidence does not support considering periodontal disease as a direct manifestation or diagnostic feature of FMF. Instead, periodontal alterations may represent increased inflammatory susceptibility associated with chronic immune activation. Future investigations involving standardized periodontal examinations, inflammatory biomarker assessment, and genetically confirmed FMF cohorts are required to clarify this potential association. [13,14,16,17,21,22] The possible involvement of maxillofacial structures in FMF appears to be uncommon but clinically relevant. Temporomandibular joint symptoms have occasionally been described as part of the musculoskeletal manifestations of FMF, particularly in patients with inflammatory arthritis. These findings should be interpreted within the context of systemic inflammatory activity rather than as isolated oral manifestations. Similarly, oral findings related to AA amyloidosis, including soft tissue enlargement or macroglossia, are rare but may indicate advanced systemic disease and require appropriate medical evaluation. The management of FMF has substantially improved with the widespread use of colchicine and the introduction of targeted biological therapies. Colchicine remains the cornerstone of treatment because of its ability to reduce inflammatory attacks and prevent AA amyloid deposition through inhibition of neutrophil activity. Although effective control of systemic inflammation may theoretically reduce inflammatory oral manifestations, direct evidence evaluating the effect of colchicine on oral outcomes is currently lacking. Similarly, IL-1-targeted therapies, including anakinra and canakinumab, have demonstrated effectiveness in colchicine-resistant FMF; however, their specific influence on oral manifestations requires further investigation. [24–27,30,31] From a clinical dental perspective, awareness of possible oral manifestations associated with FMF is important for early recognition of systemic inflammatory disease. Patients presenting with recurrent unexplained oral ulcerations accompanied by fever episodes, abdominal attacks, arthritis, or relevant family history may benefit from interdisciplinary assessment involving dental specialists, oral medicine clinicians, and rheumatologists. Recognition of potential systemic associations may prevent repeated symptomatic treatment of oral lesions without addressing the underlying inflammatory disorder. [18–20] Despite advances in understanding FMF pathogenesis, the clinical significance of oral involvement remains uncertain. The majority of available publications consist of case reports, small observational studies, and descriptive clinical observations rather than large controlled investigations.

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Consequently, important questions remain unanswered, including the true prevalence of oral manifestations, their association with specific MEFV variants, their relationship with inflammatory activity, and their potential value as indicators of disease severity. [3,8–10,18,19]

Future Perspectives

Future research should focus on establishing a more comprehensive understanding of oral involvement in FMF through multidisciplinary clinical studies integrating rheumatological and oral medicine perspectives. Prospective investigations involving genetically confirmed FMF patients should include standardized assessment of oral mucosal lesions, periodontal parameters, salivary inflammatory markers, and correlations with disease activity.|The evaluation of molecular biomarkers may provide valuable insights into whether oral tissues reflect systemic inflammatory status in FMF. Particularly, analysis of salivary cytokines such as IL-1β and other inflammatory mediators may contribute to understanding the biological relationship between systemic autoinflammation and oral tissue responses. Genotype–phenotype correlation studies represent another important research direction. Determining whether specific MEFV variants are associated with increased frequency or severity of oral manifestations may improve clinical characterization of FMF and contribute to personalized patient monitoring strategies. Further studies are also required to evaluate whether effective suppression of systemic inflammation through colchicine or IL-1-targeted therapies influences the development, recurrence, or progression of oral manifestations. Incorporating oral outcomes into future therapeutic studies may provide additional information regarding the broader clinical impact of disease control.

5 CONCLUSIONS

FMF is a hereditary autoinflammatory disorder primarily associated with pathogenic MEFV gene variants and dysregulation of pyrin inflammasome-mediated inflammatory pathways. Although oral manifestations are not considered classical diagnostic features of FMF, current evidence suggests that oral tissues may be affected as part of the systemic inflammatory phenotype of the disease. Recurrent oral ulcerations represent the most frequently reported oral finding, whereas periodontal alterations, temporomandibular manifestations, and amyloidosis-related oral changes appear to occur less commonly. These findings should be interpreted within the broader clinical context of FMF, including systemic symptoms, genetic characteristics, and inflammatory activity. The current evidence remains limited by the predominance of descriptive studies and the absence of standardized approaches for evaluating oral involvement. Further prospective investigations incorporating genetic analysis, inflammatory biomarkers, and comprehensive oral assessment are required to determine the prevalence, mechanisms, and clinical significance of oral manifestations in FMF. Improved recognition of potential oral manifestations may contribute to earlier diagnosis of systemic inflammatory disease, strengthen collaboration between dental and medical specialists, and support a more integrated approach to the long-term management of patients with FMF.

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Ethical Approval

Not applicable.

Competing Interests

The authors declare no conflict of interest.

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