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Pathogenesis of Periodontitis

Localized Periodontitis in Young Individuals: Aggregatibacter JP2 Clone, Immunological Dysfunctions and Other Stories

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ABSTRACT

Grade C molar-incisor pattern periodontitis (C-MIP) is the latest in a series of names given to a unique phenotype, characterized by an aggressive and rapid loss of tooth-supporting structures, starting early in life and usually affecting first molars and incisors. Although much less prevalent than the more generalized "chronic" forms of this disease in adults, it affects mostly young individuals of lower socioeconomic status and African descent, or from mixed-race populations, and shows a strong familial aggregation, pointing to a possible genetic contribution, yet not fully elucidated. Even though most of the studies report this disease in adolescents/young adults, it can also be diagnosed in the primary dentition, frequently in the first molar. Thus, proper periodontal examination and radiographs in children are crucial for early diagnosis and treatment. The rapid periodontal breakdown in this disease is also associated with specific microorganisms and a dysfunctional inflammatory response of the host. *A. actinomycetemcomitans* has been strongly implicated in C-MIP severity and progression, although newer technologies have pointed to the influence of other associated species implicated in this disease in different populations. Additionally, a pro-inflammatory profile along with hypo/hyperactivity of the cellular innate response has been observed in C-MIP. Genetic studies have supported evidence of family aggregation, although specific genes are yet to be identified. Several clinical therapies have been proposed to treat C-MIP over time, and non-surgical periodontal therapy with adjunctive systemic antibiotics has shown a favorable impact on clinical, immunological, and microbiological outcomes in the short and long term in both primary and permanent dentition. This paper aims to review this unique disease, its proposed pathogenic mechanisms, risk factors, treatment outcomes, and the remaining gaps that still require investigation.

1 | Introduction

Sig Socransky famously said that the form of localized periodontitis affecting first molars and incisors in young individuals was the 'Rosetta stone' of periodontology, as it almost represents a model for the 'perfect storm' of periodontitis pathogenesis. Understanding it could indeed potentially unlock some of the secrets hieroglyphics of periodontal pathogenesis. As such, efforts have been made to gain more insights into this form of periodontitis. Although studies have shed light on the particularities of this disease etiology and pathogenesis over the years, we cannot say that we have a complete understanding of it. This aims to describe the main characteristics of this disease, which has had many names over the years: 'periodontosis', 'localized juvenile periodontitis', 'localized aggressive periodontitis', and now 'grade C molar-incisor pattern periodontitis' (C-MIP), which is the term

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we will use throughout the rest of this manuscript. The following sections here will describe what makes this disease unique, the current knowledge gathered about it thus far, and what the gaps in the literature are that we are still trying to fill.

2 | Clinical Features

The uniqueness of C-MIP is due to a pattern of localization, most usually confined to first molars and/or incisors (Figure 1), as well as early onset and rapid aggressive periodontal attachment and bone loss on the affected teeth. Clinical features include:

- **Deposits**: The amount of destruction not commensurate with the amount of local irritants present, including biofilm (Figure 1) [1, 2].
- **Gingiva**: Does not usually show clinical signs of inflammation; however, in some cases and in more severe cases, the gingiva may turn red, edematous, swollen, soft and inflamed (Figure 2A) [4]. In addition, the loss of interdental papillae and sometimes tooth migration (as seen in Figures 1 and 2), common in severe cases, may lead to frequent food impaction [5]. The gingiva bleeds easily on probing, and gingival enlargement (in some cases) or recession may become evident [5].

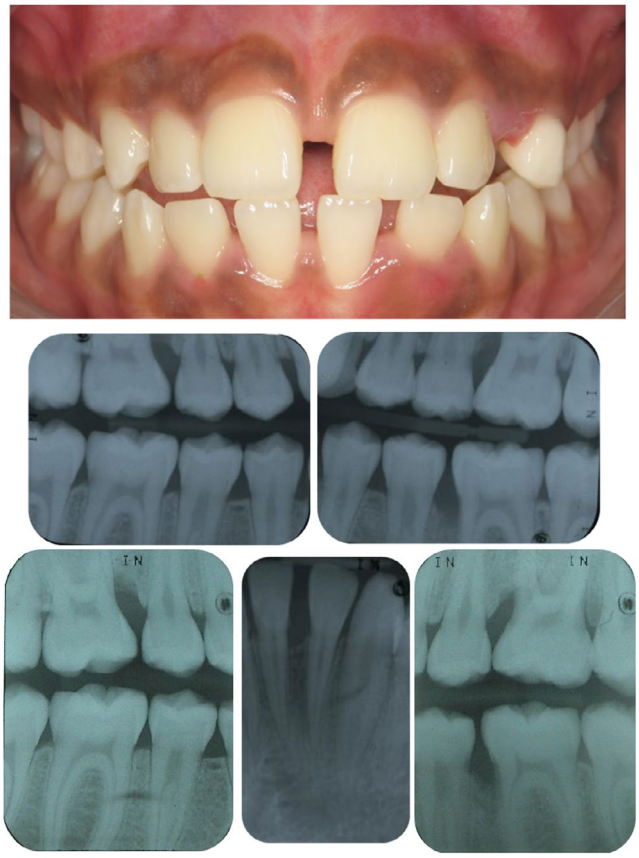

FIGURE 1 | A 12-year-old African American diagnosed with C-MIP. Minimal biofilm accumulation and low gingival margin inflammation are observed; however, bone loss and rapid clinical attachment loss can be detected at the first molars in both the upper and lower jaws.

- **Periodontal pockets**: Deep pockets of at least 6 mm surrounding affected teeth/sites [6]. In initial cases, pockets sometimes are localized on only one site, right adjacent to a very healthy site.
- **Bone loss**: Rapid and aggressive vertical or arch-shaped defects affecting primary or permanent molars [3, 4, 7–8], while horizontal bone loss is more frequent around incisors [9]. The bone loss is inconsistent with existing biofilm accumulation [6, 7]. However, the bone loss is usually bilateral and referred to as a "mirror-image pattern" [1, 10–12]. Besides vertical and horizontal bone loss, an "arch-shaped" bone loss can also be seen extending distally from the second premolars to the second molars mesially [5, 10].
- **Furcation involvement**: Class II or III involvement in multi-rooted teeth [6]. Bone loss in furcations can also be seen in primary teeth [13].
- **Primary dentition**: In case of primary teeth affected, which is not currently within the new classification, it is crucial to distinguish pathological bone loss from the physiologic process of primary tooth exfoliation and important local factors associated with the distance between bone crest and CEJ on this dentition. During normal exfoliation phase, the root apex of the primary teeth starts to resorb, as the root of the erupting permanent premolar starts to form [14]. This resorption increases as the permanent tooth becomes closer to emerging in the oral cavity, and formation of its roots increases [14]. This is distinctly different from premature exfoliation due to aggressive forms of periodontitis, where the primary tooth is exfoliated before its usual time, while its roots are usually not yet resorbing, the upcoming permanent tooth is not closer to erupting, and its roots are not yet formed (see Figure 3). Thus, there is disproportionate bone loss around these teeth compared to the rate of physiological apical root resorption and patient age. Moreover, internal and external pathological root resorptions can occur in these teeth leading to an additional signal to C-MIP diagnosis in the primary dentition (Figure 4) [13]. These pathological resorption processes may be a result of the local inflammation present around these teeth. Noteworthy, these cases do not usually present with any other systemic conditions, although some studies mention neutrophil defects may be associated with these cases [15, 16], which will be further discussed below. These characteristics should prompt the clinician to probe to confirm periodontal diagnosis [17–19]. The American Academy of Pediatric Dentistry recommends that children undergo a periodontal screening during their initial and routine dental examinations, and teeth should be probed upon first permanent molar eruption or before if any clinical or radiographic signs of disease are suspected [19]. When primary dentition is affected, it usually affects first primary molars, progress fast to the second primary molars, and sometimes incisors are also affected [13]. These characteristics should be sufficient to qualify this condition as a distinct disease entity and bring this up as a diagnostic criterion within the classification so that proper diagnosis can be made early, and treatment can be rendered at this time.

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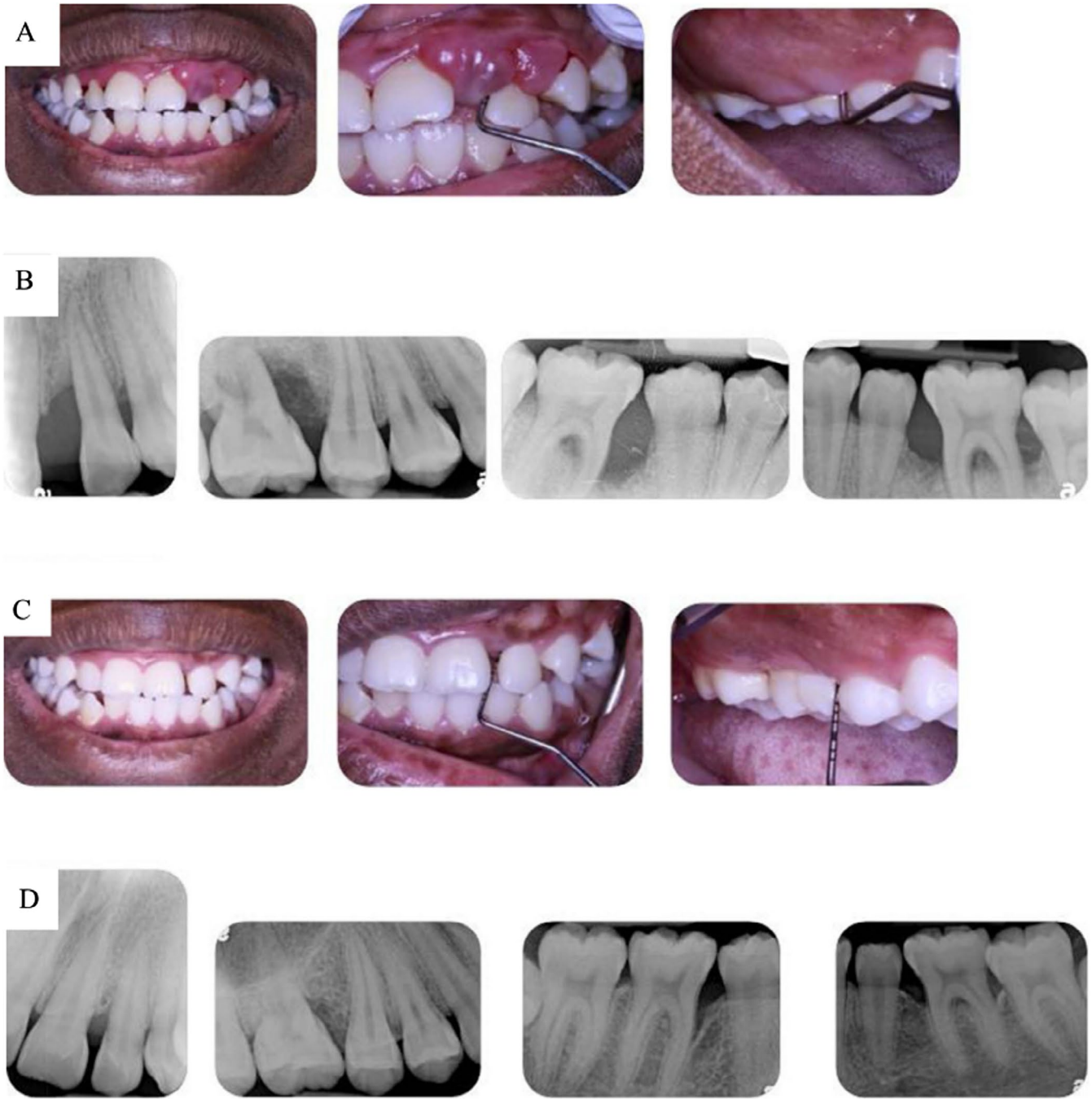

FIGURE 2 | A 14-year-old female diagnosed with C-MIP/LAP (A). Her baseline radiographic records are shown in (B). The patient underwent mechanical debridement (non-surgical treatment, NST) along with antibiotic therapy: Amoxicillin 500 mg and metronidazole 250 mg, administered three times daily for 1 week. Clinical photographs (C) and radiographic records (D) were taken 24 months after treatment *(Image Source: Miller et al., 2017* [3] Reproduced with permission from John Wiley & Sons*)*.

- **Tooth mobility** following severe bone loss [5] leading to tooth loss if left untreated [4, 17, 18, 20], And may also lead to tooth migration (see Figures 1 and 2).

- **Occlusion**: Premature tooth loss affects teeth movement and the risk of improper tooth migration and space maintenance for the permanent dentition [21]. In advanced cases where teeth have been extracted or early exfoliated due to severe mobility, malocclusion is expected, including protrusion, extrusion, migration, spacing, and flaring of teeth [6, 17], and even open or short roots of premolars in case affected primary molars are early exfoliated. Moreover, improper occlusion can cause secondary occlusal trauma due to excessive force during biting and mastication on teeth with reduced periodontium [22]. Furthermore, it is believed that vertical bone loss may be one of the consequences of occlusal trauma, as it is suggested that these forces play a role in disease progression [23, 24]. The fact that first molars and incisors are the first to erupt, and considering first molars have the bear of posterior mastication forces at approximate ages 6–11, coupled with some additional forces during the eruption

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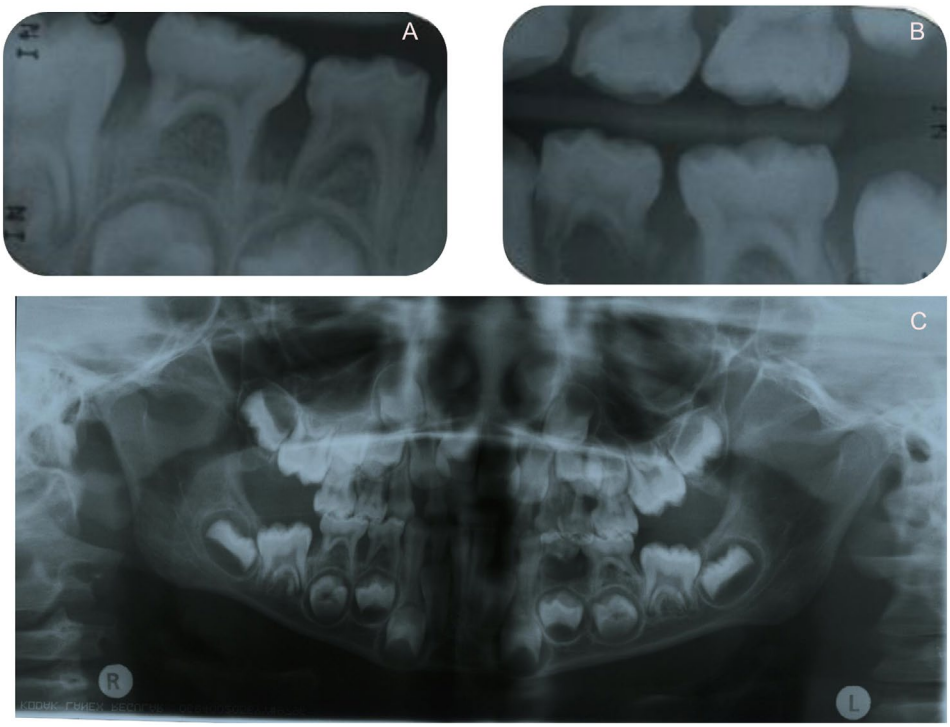

FIGURE 3 | A 6-year-old patient diagnosed with C-MIP in the primary dentition, mostly located in the first primary molars. It is possible to observe an intact root and low bone levels featuring a disease process instead of physiological exfoliation (A and B). In addition, the panoramic radiograph reveals early exfoliation timing given the patient's age, along with a lack of permanent root formation which characterizes an early exfoliation process (C). This unusual bone loss and early exfoliation pattern should be detected, and the patient should be probed to confirm the periodontal disease process for proper treatment planning.

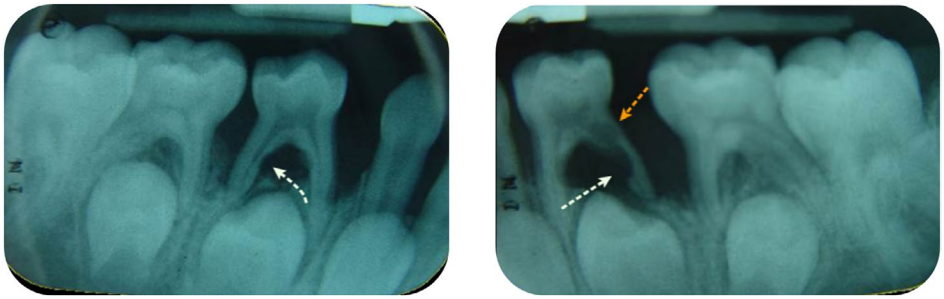

FIGURE 4 | An 8-year-old African American female diagnosed with C-MIP in the primary dentition. Radiographs reveal severe bone loss in the lower first primary molars, in addition to internal (orange arrow) and external resorption (white arrow). *(Image Source: Miller et al., 2018* [13]*).*

of second molars at around age of 12, occlusion forces may be considered here as possibly contributory to initial disease onset at these areas, at or around puberty. More discussion on this below.

Some of these features, coupled with good systemic health and strong familial aggregation, were noticed in the permanent dentition by Baer in a seminal paper over half a century ago [1].

This very specific disease pattern is very striking by its site-specificity, in the context of a clear person-specific high susceptibility. Figure 5 shows an example case of a Caucasian 16-year-old male patient affected by C-MIP. He reported a medical history of mild autism and *no known* family history of periodontitis. The patient complained about loose lower incisors and occasional bleeding on brushing. He had attended the dentist regularly since childhood and had never been diagnosed with periodontitis until recently. Clinical features show probing pocket depths > 4 mm and up to 13 mm on mandibular incisors and mesial surfaces of mandibular first molars, with *no other teeth affected*. Radiographically, extensive intrabony defects are evident on the mesial surfaces of mandibular first molars, with a combined horizontal-vertical bone loss pattern on lower central incisors. No maxillary teeth were affected. Usually, first molars and incisors are affected, and occasionally some of the remaining dentition [26, 27]. By earlier definition [6], no more than 2 teeth other than first molars and incisors are usually affected in C-MIP, although progression to affect neighboring teeth is possible in older and more severe cases [28]. The new classification does not mention these features; however, Brown et al. [28] showed that approximately 1/3 of these localized aggressive cases may progress to generalized disease. Thus, it is possible that some of these C-MIP cases may progress to generalized disease, and hence other teeth may start being affected if not treated early enough (Figure 6).

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The vertical bone loss pattern of first molars in these cases is particularly striking and has been the object of previous investigations [29, 30]. A case–control study from our research group has confirmed the specific 'arch or vertical shape' feature of such defects [29], also shown by others [12], especially when compared with the vertical bone loss of first molars of 'chronic periodontitis' cases [29]. This may be a sign of a particularly 'aggressive' bone destruction pattern compared to the slower bone destruction pattern observed in other periodontitis cases [30–32].

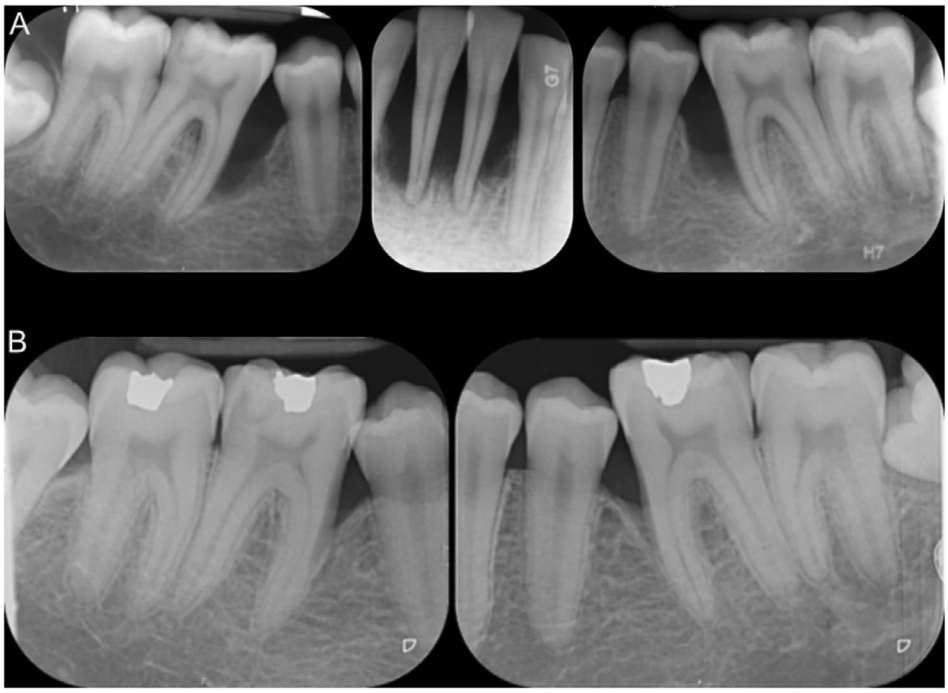

FIGURE 5 | 16-year-old male patient affected by C-MIP. Periapical radiographs show severe bone loss affecting molars and incisors (A). Considerable reductions in pocket depths and extensive clinical attachment gain in the same patient 2 years after initiation of periodontal treatment, which consisted of steps 1 and 2 periodontal therapy [25], followed by supportive periodontal care (SPC) and provision of a free gingival graft to create a band of keratinised gingiva and facilitate cleaning around the lower incisors (B).

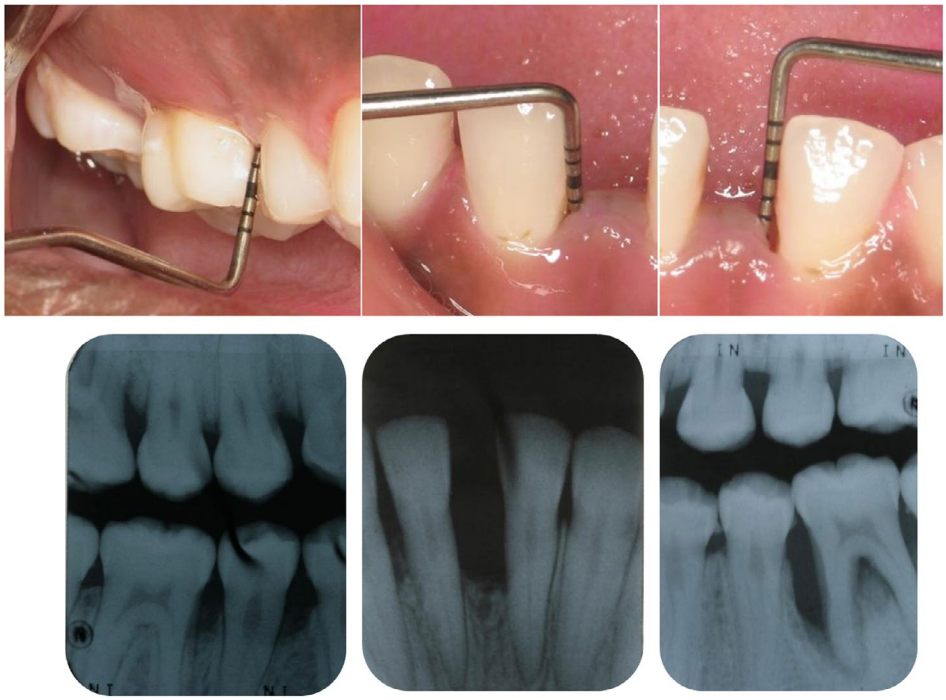

FIGURE 6 | A 16-year-old male diagnosed with C-MIP. It is possible to observe that the disease began in the incisors and molars and is starting to affect the premolars in the lower right jaw.

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3 | Microbiological Features

Host immunological response and microorganism colonization crosstalk can lead to a microbiome profile with key periodontopathogens establishing a loop between host immune responsiveness and pathogens' challenges [33]. Rapidly, periodontal tissue breakdown can be a consequence either of high-virulent pathogens or an immunological susceptibility inherited by the host, which may be particularly important for this disease condition [34]. "Early onset periodontitis" has been correlated with several pathogens such as *A. actinomycetemcomitans*, *T. lecithinolyticum*, *T. forsythia*, *T. denticola, P. gingivalis*, *P. intermedia*, *C. gracilis*, *E. nodatum*, and *F. nucleatum* [35–38]. *A. actinomycetemcomitans* has been widely studied and reported in the literature and frequently detected in this in LAP/C-MIP [35, 37, 39–42] leading to it being considered a keystone pathogen for this disease. It is strongly associated with aggressive forms of periodontitis and considered a predictor for clinical attachment loss (CAL) over time compared to unharboured *A. actinomycetemcomitans* sites [40, 43].

Depending on the lipopolysaccharide component in the bacterial membrane, *A. actinomycetemcomitans* can be classified into different serotypes (a-g) [44, 45]. Interestingly, studies have shown that serotypes may differ among diagnosed periodontitis patients based on their geographic location. The serotypes a, b, and c are the most prevalent worldwide, while the remaining ones are less frequently identified [46]. Current whole-genome sequencing analysis of *A. actinomycetemcomitans* isolates has shown that despite the phylogenetic distinctions among serotypes a, b, and c, there is a close relation between serotypes b and c after careful phylogenetic tree assessment. On the other hand, serotype a seems to be distantly related to both mentioned serotypes [46]. Aggregatibacter JP2 clone (serotype b) has been strongly correlated with aggressive forms of periodontitis and highly identified in different populations, with a high prevalence in African descendant populations. This serotype's spread from Mediterranean Africa to the Western Africa and America continents could have been related to migratory activities since the 16th century [44]. In contrast, serotype b prevalence has not been observed in specific geographic areas such as Europe and Asia [47–49]. Kim and collaborators have shown a higher detection of serotypes b (33.3%), c (25%), and a (20.8%) in German patients, while serotype c (61.9%) and d (19%) were more prevalent in Koreans diagnosed with the old "aggressive" or severe chronic periodontitis [50]. The same pattern for the prevalence of JP2 clone identification for Thai subjects was reported, where the prevalence of *A. actinomycetemcomitans* was reported but not the JP2 clone [49]. The tropism of *A. actinomycetemcomitans* serotype b in some populations may indeed support the hypothesis of a host genetic role for this specific microorganism colonization and disease development [51].

Along with its reported high prevalence in this disease, specific characteristics and virulence factors pertaining to *A. actinomycetemcomitans* have given it the role of keystone pathogen for this disease [39, 52–55] (Figure 7). Beyond the tissue invasion properties [56–58] and specific proteins capable of epithelial disruption [59, 60], JP2 clone enhanced leukotoxin (LtxA) activity plays a significant role in the host immunological system response [61], especially in neutrophil degranulation and IL-1β release by macrophage after inflammasome activation [55, 62]. In addition, LTxA activity also induces hypercitrullination in neutrophils [63], which could potentially connect this C-MIP key pathogen with autoimmune diseases such as rheumatoid arthritis [63–65]. However, it is important to highlight that citrullination is not solely dependent on bacterial activity; rather, it also depends on interactions with components of the host immune cells [63]. Also, hypercitrullination in neutrophils has not been reported in C-MIP subjects. *A. actinomycetemcomitans* JP2 clone higher leukotoxicity has been associated with the deletion of 530 base pair (bp) in the *ltxCABD* promoter [66]. In addition, studies have shown that not only bp deletion is correlated to increased leukotoxin activity [67], but also the insertion of 886 bp to *ltx* promoter [68]. The LtxA release occurs by a Type I secretion system and depends on other proteins from the RTX family such as LtxB, LtxD, and TdeA [61]. Not only do RTX family proteins have an impact on LtxA release, but free iron also significantly influences this process [69]. Cytolethal distending toxin (CDT) is a bacterial protein exotoxin expressed in some gram-negative species with a significant role in host immunological disturbance [46, 70] including DNA damage [71], immunological cell cycle arrest [72] and pro-inflammatory cytokine release [73]. On average, 66%–78% of *A. actinomycetemcomitans* serotypes express CDT under periodontitis condition [74–76] and it is the only known oral microorganism among periodontopathogens to have this property [46]. In fact, *A. actinomycetemcomitans* with the CDT genotype has been highly detected in aggressive forms of periodontitis [77]. Moreover, it is worthy to mention that *A. actinomycetemcomitans* LPS for each serotype has a distinguished virulence activity targeting several cells including epithelial cells [78, 79], gingival fibroblast [80, 81] and other innate immune cells [82, 83].

JP2 clone is highly associated with aggressive forms of periodontitis (RR = 1.86) and disease establishment overtime (RR = 4.12) [84]. As previously mentioned, this strain was exclusively associated with North and West African populations diagnosed with early-onset periodontitis [62]. Several studies in the Morocco population have shown a high association of C-MIP/LAP development and progressive CAL over time in subjects positive for JP2 [43, 85–86]. However, due to migratory activities, this strain has also been reported in other locations such as North and South American populations under early-onset periodontitis [40, 59, 62, 87–88]. Although most studies have reported robust evidence of LAP/C-MIP prevalence with JP2 clone in African descendants, Claesson et al. revealed that this strain was also observed in Caucasians with LAP/C-MIP [89, 90]. Although *A. actinomycetemcomitans* has been considered one of the most important pathogens in this disease, the interplay between it and *S. parasanguinis* and *F. alocis* may sustain the risk of CAL over time in initially healthy sites [41]. This certainly needs to be further explored. In fact, *A. actinomycetemcomitans* establishment in the biofilm environment requires some specific conditions such as early lactate producer colonizers, which support a consortium for growth and virulence activity [39]. Razooqi et al. recently reported that synergistic activity between *F. alocis* and non-JP2 genotype *A. actinomycetemcomitans* resulted in progressive CAL, even in low bacterial load, after a 2-year follow-up in a Ghanaian cohort [91]. Despite the reported activity of *A. actinomycetemcomitans* in localized aggressive forms of

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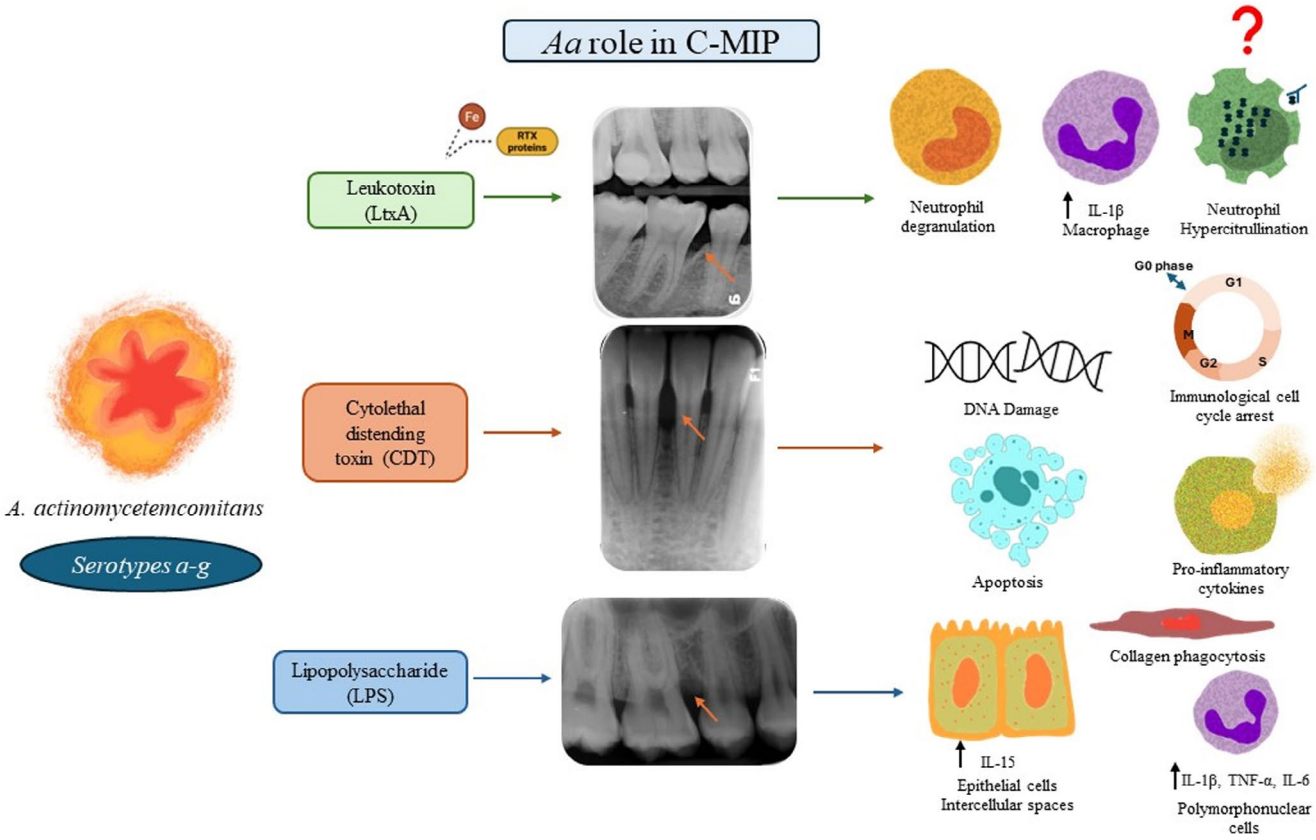

FIGURE 7 | Schematic figure displaying *A. actinomycetemcomitans*' unique virulence mechanisms and factors along with host immunological response against it.

periodontitis, *P. gingivalis*, *T. forsythia*, *T. denticola*, *C. gracilis*, *E. nodatum*, *F. alocis*, *Tannerella sp, P. micra*, and *P. intermedia* have also been described as part of the complex bacterial profile in this disease [37, 38]. Throughout different populations, *A. actinomycetemcomitans* seems to be a common species associated with this disease, but different populations may show some different associated species. For instance, a Brazilian research group [38] showed the occurrence of *P.gingivalis* whereas a North American group [37] showed *F. alocis* and others but not *P.gingivalis*. Thus, the microbial *community* associated with this disease needs to be further elucidated in the different populations.

As mentioned earlier, this localized aggressive disease, C-MIP, may affect both primary and permanent dentitions. From a microbiological point of view, *A. actinomycetemcomitans* early colonization [92] can be associated with diseased development in early ages including primary and mixed dentitions [3, 13]. The early colonization of relevant periodontopathogens such as *A. actinomycetemcomitans* in children and young adults in primary and mixed dentition can be explained by the vertical transmission of pathogens from relatives. Monteiro et al. [93, 94] have shown that children from parents diagnosed with the generalized aggressive form of the disease presented a higher frequency of *A. actinomycetemcomitans* in both oral biofilm and saliva compared to children with non-periodontitis diagnosed relatives. Moreover, the same research group has reported a similar beta-diversity profile between diagnosed parents and their healthy offspring carrying a large core of species correlated with periodontitis such as *Filifactor alocis*, *P. gingivalis*, and *Fusobacterium nuclatum* [95]. Even after a 3-month professional biofilm control protocol with a reduced plaque index at the end of the follow-up, children from parents diagnosed with aggressive forms of periodontitis presented a resilient microbiome profile composed of relevant periodontopathogens [95]. This outcome reinforces an important role that host susceptibility and genetic inheritance patterns play in microbiota composition [96, 97].

A. actinomycetemcomitans was reported to be negatively correlated with age ($r = -0.74$, $p = 0.001$) in a previous LAP/C-MIP study [38]. Jensen et al. evaluated its presence in 513 children from Morocco (50.3% female, age range: 7–10 years) [85]. Regarding primary dentition, 5 out of 75 children that were included in the clinical examination (6.7%) had CAL ≥ 3 mm at least in two sites, along with the presence of JP2 genotype. This clinical association was not found in cases with the *A. actinomycetemcomitans* non-JP2 genotype or when *A. actinomycetemcomitans* was not detected. Additionally, the same association between having at least two periodontal sites with CAL ≥ 3 mm and the presence of the JP2 genotype was not observed in the permanent first molars [85]. Radiographic bone loss was detected in primary dentition sites from 8 out of 64 children with a positive association with JP2 genotype presence [85]. Similarly, Aberg et al. have shown that either JP2 (OR = 14.3; 6.2–33.1) or non-JP2 genotypes (OR = 3.4; 2.0–5.8) of *A. actinomycetemcomitans* were predictive for CAL ≥ 3 in young Ghanaian adults after 2 years follow-up [98]. This strain has a strong stability over time, and its potential infection increases the relative risk

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of aggressive form of periodontitis (RR = 13.0, CI 9.0–21.4) [86]. Considering *A. actinomycetemcomitans* and other periopathogens' role in C-MIP development, microbiome composition from diagnosed patients under primary/mixed and permanent dentitions has been recently investigated [99]. *A. actinomycetemcomitans* was found in high prevalence in this disease in both primary and permanent dentition (85.7% and 71%, respectively), and a few other pathogens were identified in both these dentitions (e.g., *Campylobacter*, *F. nucleatum*, and *G. morbillorum*) [99]. However, a distinguished microbial profile was at first observed between these two affected dentitions. An increased frequency of *Capnocytophaga*, *Leptotrichia*, and *Streptococcus* genera was detected in the primary dentitions, whereas a mature microbiome composition featured by *F. alocis, T. forsythia*, and *Synergistetes* sp. was highly abundant in the permanent dentition both affected by C-MIP [99]. Although primary dentition microbiome analysis displayed pathogens correlated with both healthy and periodontitis conditions, this study emphasizes the role of *A. actinomycetemcomitans* in C-MIP disease and its impact from early ages [99].

Recognizing that C-MIP can be diagnosed in the primary dentition led us to consider a possible initial development of the disease during this early life stage [3, 13, 100–101]. First and second molars have been identified as the most affected type of teeth in this dentition [12, 102] along with the distal area of the maxillary canine [12, 102] under this condition, possibly starting at first primary molars and then progressing to second primary molars [12, 13]. Furthermore, a high frequency of *A. actinomycetemcomitans* has been reported in primary dentition sites, either preceding the disease [92, 98, 103] or during its progression to severe periodontal breakdown [85, 99, 104]. Thus, it appears that the microbiological features inherent to this pathogen (e.g., tissue invasion and pockets recolonization) [56, 105] may play a significant role in the progression of C-MIP disease in susceptible hosts, leading to possible disease recurrence and progression to the permanent dentition if left untreated [3, 106–107]. Interestingly, the influence of this key pathogen in generalized forms of aggressive periodontitis is not as pronounced as in localized cases [108]. This may be attributed to the progression of localized early-onset aggressive periodontitis to new sites in the long-term [28], resulting in a generalized manifestation of the disease sustained by other microorganisms from the red/orange complex [108]. C-MIP subjects seem to display a less diverse microbiome composition compared to generalized aggressive forms [109], which may explain the major impact of some specific microorganisms, like *A. actinomycetemcomitans*, on disease initiation and maintenance over time.

Studies have shown that certain viruses might play a role in early-onset periodontitis [110, 111]. Not only can viruses indirectly influence disease progression by impairing the immune response [110] and cell infection followed by bystander activation (one of the mechanisms to develop autoimmunity) [112, 113], but a synergistic interplay may also occur among periodontopathogens such as *A. actinomycetemcomitans* and *P. gingivalis* and viruses (e.g., Cytomegalovirus and Epstein–Barr virus) [110, 114]. Herpesvirus glycoproteins surrounding infected membrane cells [115] can increase the bacterial adherence to its surface [116], potentially enhancing the activity of periodontopathogens such as *A. actinomycetemcomitans* and *P. gingivalis* [116]. A coexistence between virus infection and periodontopathogens can enhance the chance of tissue breakdown due to bacterial and virus virulence factors such as herpetic lytic infection [116, 117] and *A. actinomycetemcomitans* LtxcA and CDT [116]. Although the role of viruses in the pathogenesis of periodontitis remains controversial [118]. While some studies have reported that certain viruses are frequently associated and detected in the subgingival biofilm of C-MIP individuals [119, 120], others have shown very low prevalence in disease with no significant difference compared to healthy individuals [118]. The impact of viruses on the host immunological system indirectly affects its response against microbiota dysbiosis, which may increase the risk of periodontitis development and progression [121, 122]. Thus, further and possibly longitudinal studies should be carried out to better understand the interplay between viruses and early onset periodontitis.

4 | Genetics and Host Response

Lehner et al. (1974) were probably the first to identify some specific immunological features of 'juvenile periodontitis', such as selective cell-mediated immunodeficiency, impaired stimulation of lymphocytes, and inability to mount the normal defensive reaction to Gram- bacteria [123]. They suspected a similar pathogenesis to chronic periodontitis, but accelerated by hypothetic 'migration inhibitory factors', lymphotoxins, and bone resorption factors. Instead of a total immune deficiency, this study proposed a regulatory dysfunction in which immune cells can respond but are actually somewhat inhibited by serum components [123]. Other studies later confirmed some chemotaxis defects in neutrophils in families with C-MIP [15, 16]. These studies were the first to suggest that C-MIP may develop based on bacterial infection combined with altered immune regulation, which weakens the affected apparatuses' ability to properly combat oral pathogens, resulting in aggressive breakdown.

Not only have chemotaxis issues been implicated for neutrophils, but these cells' hyperresponsiveness has also been indicated as an important mechanism in the pathogenesis of C-MIP, leading to excessive soft tissue loss [124]. Studies have reported conflicting evidence that neutrophils had functional impairment or deficiency in C-MIP [125, 126] or a hyperactivated state in some cases [124], which leads to increased higher levels of reactive oxygen species (ROS) and abundant proinflammatory mediators [127, 128]. It seems that an up- and downregulation of the innate immunological system is a key host characteristic under this disease challenge, featuring immunological dysfunction. Signal transduction abnormalities in neutrophils from patients with C-MIP include decreased intracellular calcium levels, reduced protein kinase C (PKC) activity, and increased diacylglycerol (DAG) levels, impairing chemotaxis while enhancing oxidative burst activity [124]. In addition, there are also altered lipid mediator profiles of these neutrophils generating high levels of prostaglandin E2, leukotriene B4, and lipoxin A4 that will impact the inflammatory response [124, 129]. This hyperactive state of neutrophils results in the secretion of excessive amounts of extracellular enzymes like elastase and collagenase, leading to connective tissue and alveolar bone degradation [130, 131]. In the same context, Shaddox et al. [132] also reported in a cohort of 30 C-MIP patients a hyper inflammatory responsiveness of

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whole blood cells to LPS stimulants. Interestingly, C-MIP individuals rely on this exacerbated response regardless of the biofilm composition (from a healthy or diseased site) [133]. Thus, it seems that the host's immunological predisposition to microbiological challenges is greater than the microbiota composition itself. The immune response to periodontitis preserves some relatively quite different yet interrelated aspects; this involves an exaggerated immune response to periodontal pathogens contributing to disease progression, and possibly a differentiated treatment response [134].

Several studies also investigated total antibodies' levels (e.g., IgG, IgM, and IgA) [123, 135–139] as well as specific antibodies against periodontopathogens in the pathogenesis of C-MIP including *A. actinomycetemcomitans* [140–142], *P. gingivalis* [140–142], *B. fragilis* [140], *P. intermedia* [141, 143], *C. rectus* [143], *E. corrodens* [143], *F. nucleatum* [143], and *C.ochracea* [141]. Some of these studies suggested a systemic immune response expressed by elevated serum total IgG [123, 140, 144], IgG to *A. actinomycetemcomitans* [141–143] *and P.gingivalis* [141, 143] in C-MIP, while others reported no significant differences [135, 139, 145]. Some studies also suggested a racial difference in antibody response with greater IgG levels in African American subjects compared to Caucasians [135, 146]. The role of elevated titers of specific antibodies against pathogenic microorganisms in C-MIP has been controversial, particularly their diagnostic and prognostic significance [146]. This increased immune reaction indicates ongoing exposure to bacteria and the body's attempt to combat the infection [147]. Nonetheless, some argue that increased antibodies do not necessarily indicate protection [148, 149] and may instead stem from persistent infection or immune dysfunction [97, 150–151]. Furthermore, some biomarkers, such as IgA [123, 140] and IgM [123, 140] and IgG [152, 153] to *A. actinomycetemcomitans* [140, 142, 154] and *P.gingivalis* [153], occur in higher concentrations in C-MIP, making their role in disease pathogenesis more complex. Despite these findings, the long-term high titers of antibodies following treatment [155, 156] render them questionable as markers of disease resolution. Thus, while antibody profiles provide insights into host-microbial interactions, their specific role in C-MIP remains to be elucidated.

Genetics plays an essential role in the susceptibility of C-MIP [157, 158]. Patients with a family history of C-MIP or generalized aggressive disease (now termed grade C) are more prone to develop C-MIP [1, 159]. A systematic review conducted in 2019 reviewed 13 studies that investigated the relevance of familial aggregation to the development of C-MIP in young subjects and found that more than half of the studies showed a positive association [160]. Heritability of susceptibility genes from parents with C-MIP increases the children's susceptibility to developing C-MIP [161–163] although it is difficult to quantify heritability in these cases. It is believed that having a particular predisposing gene does not necessarily lead to C-MIP; it mainly increases the risk, as periodontitis is a multifactorial disease, meaning the presence of more than one factor is essential for disease initiation [164–166]. Overall, it appears that genetic predisposition to C-MIP is quite heterogeneous [167]. It is still unclear if some or all C-MIP cases may be inherited as single gene defects rather than as polygenic defects, as for most common forms of periodontitis. Marazita and collaborators [168] investigated genetic inheritance patterns for early-onset periodontitis using mixed model segregation analysis. Despite the inclusion of both localized and generalized cases in the analysis, along with the use of a lenient criterion for diagnosing periodontitis in C-MIP proband relatives, the authors concluded that an autosomal major locus (a single gene located on a non-sex chromosome with a significant effect on the trait) could explain the patterns of early-onset periodontitis observed in families. Moreover, a dominant mode of inheritance was identified in this study, regardless of race, supporting the family aggregation [168]. However, it is important to highlight that no genetic diagnostic test emerged of clinical value for periodontal diagnosis, prevention, or prediction of disease resolution [167]. In another study [169], 55 patients with aggressive periodontitis (not necessarily C-MIP) and 100 of their first-degree relatives were clinically examined, and it was reported that 10 out of the 100 had the disease [169]. In a Florida cohort [12], of 78 families with at least one affected sibling, there were a total of 243 siblings, of whom 138 (57%) were affected with C-MIP.

5 | Theory of Pathogenesis: Is C-MIP a Distinct Form of Periodontitis?

As the name implies in C-MIP, the disease pattern mainly affects molars and incisors as they are the first teeth to erupt in the oral cavity and build up biofilm that triggers the inflammatory host response [13]. Longitudinal studies are needed to understand better why certain teeth are affected [170]. However, in the primary dentition, the disease may be more commonly restricted to molars [13], unlike the permanent dentition, where the disease initially affects incisors and first molars, first molars only, or incisors only [12], before progressing to involve more teeth, in some cases [171]. It has been reported that primary first molars seem to be the most affected teeth with severe bone loss that extended within a year to involve the second primary molar [13], whereas, in the permanent dentition, this progression does not happen as rapidly and not in all individuals [28]. Miller et al. [13] suggested that the disease would extend from the primary first molars to the primary second molars within 12 months, as the primary second molar erupts shortly (within 12 months) after the first primary molar, unlike in the permanent dentition, where permanent second molars erupt years after the first permanent molars. The fact that the disease in primary dentition does progress quite fast to the second primary molars could indicate a progression to the first permanent molar, which erupts around the age of 6, if left untreated. As mentioned before, this disease in primary dentition also harbors a high frequency and abundance of *A. actinomycetemcomitans*, which is known to invade tissues [56, 105, 172]. Thus, if left untreated, the infection could progress to the first permanent molars with time. Another hypothesis is the fact that first molars and incisors are the first teeth to erupt in the mouth. Since these individuals have a higher susceptibility to this disease, an apparent hyper-inflammatory response to LPS [132] along with an innate and adaptive immune system under development in early ages [173], biofilm accumulation in these sites could lead to the breakdown of the disease in these teeth first.

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An alternative theory for the molar-incisor pattern suggests that early childhood infections with Cytomegalovirus and Epstein–Barr virus may contribute to defective root cementum formation [110]. These viral infections are common in early stages of life [174, 175] and may interfere with the odontogenic process leading to impairment in odontoblasts and ameloblast differentiation, as reported in in vitro models [176]. Studies have reported that cementum hypoplasia in teeth from patients diagnosed with LAP/C-MIP may be associated with the initiation and progression of the disease [177–179]. Lindskog and Blomlöf [179] observed cementum hypoplasia in molars of four patients with LAP/C-MIP compared to healthy controls. Not only was this cementum disturbance observed in areas associated with bone loss but also in the interalveolar part of the root, which may support the hypothesis of hypoplasia rather than being a consequence of the disease or treatment [179]. Paknejad et al. have observed a similar finding on the mesial roots of first molars in LAP patients compared to controls [180]. In addition to that, more severe cementum defects have been reported in aggressive forms of periodontitis than in the previous chronic periodontitis or gingivitis [181]. The absence of proper cementum extension and matrix composition may impair tooth attachment to the bone via Sharpey's fibers. This anatomic impairment may potentially facilitate local and deeper microbial colonization along with disease progression [179, 181]. It is important to highlight that few studies of a limited nature have been conducted on this topic and more extensive controlled studies are required to support this hypothesis. It is acknowledged that investigating this hypothesis is difficult due to the temporal association of the anatomical issue with the actual development of the disease (Figure 8).

In terms of disease extent, a systematic review found that localized C-MIP had a higher prevalence than generalized in young subjects (≤25 years old) [160], contrary to another study that concluded that localized and generalized forms of the disease had a similar range of prevalence of 0.01%–4.3% and 0.02 to 4.3%, respectively [182]. Localized aggressive forms of periodontitis have been more prevalent in African populations (1%–5%) and in the Middle East (4.4%) and mixed-population regions such as South America (0.3%–2%). Fewer cases have been observed in Caucasian populations [163, 183]. Some studies have reported a lower prevalence of generalized forms of early-onset periodontitis compared to localized forms in African and Middle Eastern regions [184–187]. This low prevalence may be associated with the lower rate of progression from the localized to the generalized form of the disease (approximately one-third), as mentioned by Brown et al. [28] A definitive progression cannot be ascertained, as the extent of the disease depends on the age at diagnosis since C-MIP tends to be localized at an early age and more generalized when the disease progresses and extends at an older age, at least in a few cases [188]. So, in conclusion, is C-MIP a distinct form of periodontitis? Considering the site-specific nature of this disease, its rapid and severe progression in young adults, including those even in primary dentition, along with the mentioned microbiological factors (e.g., *A. actinomycetemcomitans*-specific

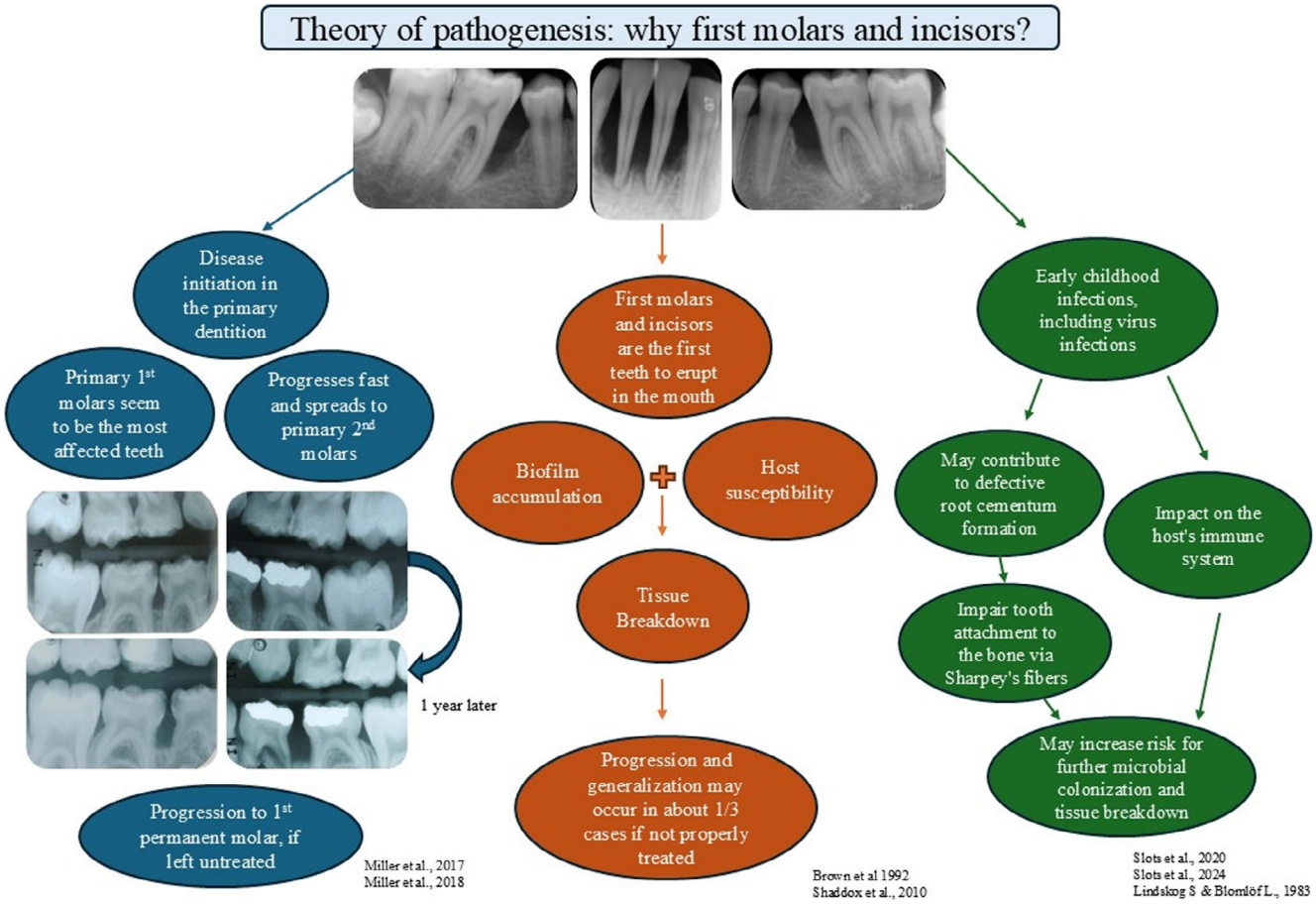

FIGURE 8 | Diagram representing current hypotheses for the disease molar incisor pattern.

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activity/toxicity) and immunological dysfunctions (e.g., hyper-responsive inflammatory profile, hyper/hypo neutrophil activity), C-MIP can be stated as a unique form of periodontitis, especially based on its clinical features.

6 | Short- and Long-Term Outcomes in C-MIP Individuals After Treatment

Non-surgical therapy (NST) based on subgingival instrumentation combined with systemic antibiotics (ABX) is the most recommended clinical approach to treat LAP/C-MIP [3, 38, 59, 189–194] (Figures 2 and 5). Both in the short or long term, NST + ABX (Amoxicilin—AMX and Metronizadole—MTZ) has a positive effect on CAL gain and PD reduction [3, 59, 190, 194] followed by host immunological modulation [192, 195–196] and microbiological shift towards eubiosis [36]. In the short term, Van Winkelhoff et al. have shown that NST + ABX (250 mg-MTZ + 375 mg-AMX 3× daily for 7 days) resulted in 1.67–2.20 mm PD reduction after 9–11 months, even in patients that experienced previous periodontal treatment [197, 198]. Moreover, a significant reduction in *A. actinomycetemcomitans*, *B. intermedius, P. gingivalis*, and *P. intermedia* was also detected in LAP/C-MIP-diagnosed patients after cultivation and isolation microbiological method [197, 198]. With a different ABX posology (400 mg-MTZ and 500 mg-AMX 3× daily for 14 days), Rebeis et al. reported great PD reduction and CAL gain in LAP/C-MIP affected sites with higher values for deep sites after 1 year follow-up. Considering host modulation, reduced IgG serum levels for surface protein Omp29 and a/b *A. actinomycetemcomitans* serotypes were detected in LAP/C-MIP-diagnosed subjects after 1 year post-treatment [59]. Despite the posology reduced from 14 to 7 days, Martins et al. showed benefits under this combined clinical approach leading to 1.03 mm-PD reduction and 1.01 mm-CAL gain 1 year later [190]. In addition, IL-1β at local (gingival crevicular fluid—GCF) and serum levels were reduced after treatment. In serum levels, IL-17 ($r = -0.55$) and MCP-1 ($p = 0.77$) were correlated with PD reductions while IL-1β with BoP reduction ($r = -0.68$) in C-MIP/LAP diagnosed individuals. In GCF levels, IL-1β was negatively correlated with CAL gain ($r = -0.68$) [190]. Based on this correlation analysis, it appears that host hyper-responsiveness can guide the clinical success of this therapy. Allin et al. showed that patients with high INF-γ, IL-6, IL-12p40 levels after LPS-blood stimulus at baseline had an inferior treatment response, with higher PD > 4 mm percentages sites and increased PD and CAL when compared to those with mixed high-low and low cytokines after 1 year of follow-up [134].

Not only did NST + ABX lead to a positive clinical outcome in C-MIP-diagnosed patients in permanent dentition, but also in young adults under primary dentition [194]. Merchant et al. showed greater PD reduction (2.25 mm) and CAL gain (3.04 mm) in primary dentition after NST + ABX (250 mg-MTZ and 500 mg-AMX 3× daily for 7 days) when compared to the permanent ones (PD reduction = 1.82 mm, CAL gain = 1.84 mm) after 1 year post-therapy [194]. The favorable profile for NST + ABX displayed by younger adults diagnosed with C-MIP may be associated with their lower complex-dysbiotic microbiome profile [99], as mentioned above, along with a different inflammatory response in children [199] even under the disease challenge, according to preliminary data [200]. After LPS-blood stimulus from C-MIP individuals diagnosed in primary dentition, it was reported that most cyto/chemokine levels from young adults were down-regulated compared to those under permanent dentition [200]. Despite the lack of prospective cohort studies evaluating C-MIP incidence in the permanent dentition after disease diagnosis and management in the primarydentition, there are a few studies indicating a possible benefit of early intervention. After NST + ABX, Bimstein showed that only one young adult, out of 10, diagnosed with disease in the primary dentition, had disease recurrence 7 years post treatment in the permanent dentition [107]. Likewise, Mros and Berglundh have shown a low disease recurrence rate (2 out of 11) of C-MIP patients treated by NST in 14–19 years of follow-up without a specific periodontal maintenance appointment [106]. Conversely, retrospective radiographic analysis reported that 18 out of 20 patients diagnosed with C-MIP in the permanent dentition had previous signs of the disease (radiographic bone loss) around the first and second primary molars [3]. Similar results were also reported by Cogen et al. [101]. Robust evidence to prove this is surely difficult to produce, given ethical issues regarding treatment. However, it seems reasonable to assume that periodontal probing examination in children followed by early intervention in case of C-MIP in primary dentition could indeed prevent the re-occurrence of the disease in the permanent dentition [201, 202].

Considering NST + ABX outcomes in a long-term, Branco-de-Almeida et al. [192] and Miller et al. [3] observed that clinical benefits achieved with this approach were maintained up to 2 and 4 years after treatment, respectively. In fact, Miller et al. reported that all patients presented over 50% reduction of affected sites (PD > 4 mm and CAL ≥ 2 mm) 4 years post-treatment [3]. Likewise, considerable PD reduction and CAL gain were observed in affected sites by Branco-de-Almeida at 2 years follow-up while local inflammatory biomarkers were also regulated in the long term [192]. At least in one time point assessed, IL-12p70, IL-2, IL-6, MIP-1α, RANKL, and OPG concentration levels reduce in C-MIP disease sites. Moreover, a similar immunoinflammatory profile was detected between healthy and LAP/C-MIP 1 year after treatment [192]. Focusing on microbiological shift after therapy, a notable impact on JP2 genotype frequency after NST + ABX (250 mg-MTZ and 500 mg-AMX—3× daily for 7 days) was observed by Burgess and collaborators, as assessed by PCR analysis [191]. Not only were JP2 genotypes undetected in healthy sites from diseased patients one year post-treatment, but they also decreased to 3.23% in C-MIP affected sites. Moreover, positive/direct correlations between CAL ($r = 0.3619$) and PD ($r = 0.2889$) with JP2 frequency were also observed in this study ($p \leq 0.002$) [191]. Veslko et al. have shown that the same NST + ABX approach also impacted microorganism prevalence and abundance up to 2 years follow-up [36]. Higher health-associated species (*R. dentocariosa/mucilaginosa*, *S. anginosus/gordonii*, and *P. oulora*) were detected in the C-MIP group in relation to baseline, including a similar profile with healthy sites starting 6 months following treatment. Well-known periodontopathogens such as *A. actinomycetemcomitans*, *F. alocis*, *T. forsythia*, and *C. gracilis* were reduced after 3 months post-therapy. Although a rebound was observed 6 months after treatment, these microorganisms' prevalence continued to decrease until 2 years [36]. Together with the clinical advantage shown

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above, this combined clinical approach was also able to modulate the C-MIP microbial profile close to healthy sites.

Following the study's timeline on LAP/C-MIP treatment, surgical procedures were widely performed in the past to treat LAP/C-MIP with good clinical outcomes [42, 203–207] However, based on the clinical and microbiological improvements, including long-term stability, achieved with a less invasive therapy (NST + ABX), with one course of ABX therapy, the surgical approach has not been currently considered the first treatment of choice to tackle this disease, although surgical intervention may still be needed in a few cases of severe remaining defects. Miller et al. [3] reported roughly 10% of patients needed surgical intervention following NST + ABX in a cohort of 145 C-MIP patients. Moreover, a better microbiological outcome based on *A. actinomycetemcomitans* reduction can be achieved using ABX therapy in the long term [36] rather than by the surgical procedure alone [204]. Nowadays, surgical procedures are mostly performed in cases of residual PD along with BoP or remaining intrabony defects in LAP/C-MIP, focusing on periodontal regeneration. Despite the limited number of studies on regenerative therapy for localized aggressive forms of periodontitis, some case reports have shown favorable long-term outcomes [208, 209]. However, more clinical studies should be carried out to reinforce this evidence in localized aggressive forms of periodontitis.

Gender impact on C-MIP prevalence and therapy outcome is still a topic under discussion. Tavakoli et al. showed a different GCF profile as well as systemic inflammatory response to LPS between females and males with C-MIP [210]. Interestingly, a hyperinflammatory profile in the GCF of C-MIP males was reported, including greater levels of TNF-α, IFNγ, MCP1, and MIP-1α. In addition, C-MIP male healthy sites showed high IFNγ compared to C-MIP healthy females' sites. On the other hand, a hyperresponsive profile was observed in C-MIP females after LPS-blood stimulus. *P. gingivalis* LPS induced higher levels of eotaxin, IFN-γ, and GM-CSF, while *E. coli* LPS resulted in increased GM-CSF and IFN-γ concentrations in females [210]. A distinguished systemic inflammatory profile was observed between C-MIP females and males ($p = 0.007$) [210]. Thus, it appears that there may be a differential inflammatory profile of this disease between males and females, although prevalence studies do not confirm a higher prevalence in either sex [163, 168, 211]. Thus, new studies should be carried out on this topic to correctly address the female and male inflammatory profile under C-MIP diagnoses towards better disease comprehension and individualized clinical management. Overall, the literature points towards favorable treatment outcomes in C-MIP, particularly if the disease is caught early and managed long-term with strict supportive care in both sexes.

7 | Limitations of Current Evidence and Future Directions

Although several studies have shown relevant characteristics of C-MIP disease focusing on better clinical diagnosis and approach, further evidence needs to be provided for improving our understanding of this unique disease. Despite the well-known heightened inflammatory profile in C-MIP patients, there is not a consensus in the literature about specific biomarkers to feature this disease diagnosis and progression, compared to other forms of disease [144]. However, despite a similar pathogenic endpoint (i.e., high levels of similar inflammatory cytokines or periodontopathogens found in the sites with disease) in the different forms of periodontitis, the rapid progression rate seen in these young individuals with a very unique clinical pattern certainly points to a differentiated susceptibility and pathogenic pattern here that certainly deserves further elucidation. A deeper investigation of these specific characteristics that influence the onset and trajectory of this disease will provide clinicians with a better and individualized treatment plan design, preventive strategies, and supportive therapy for these highly susceptible individuals and families. Although some studies have shown a distinguished C-MIP microbiome profile either in primary or permanent dentition [99], there are other factors, such as metabolites, proteins, and host genetic factors, that may contribute to this disease's challenging course. The advances of omics technology in our field may indeed provide us with new tools and new insights into this disease to enhance its diagnosis and treatment plan towards new targets. Despite evidence of C-MIP diagnosis in the primary dentition, only retrospective studies are available to provide a possible association between untreated cases in children and progression to the permanent dentition in young adults [3, 13]. As mentioned previously, this is a difficult point to prove with robust studies, given its ethical limitations. However, prospective studies should be carried out on this topic to provide more evidence on early treatment and long-term evaluations of this disease. Although relevant C-MIP genetic features have been published [212], there are still several “gray areas” (e.g., gene variation, family trait, and single nucleotide polymorphisms) that should be investigated to better understand certain specifics on the host susceptibility markers. This might be addressed in the future by genome-wide association studies with a higher sample size integrated with other omics techniques to encode particular host risk to this disease considering confounding factors. Considering treatment approach, NST + ABX is the current less invasive and very effective approach to treat C-MIP patients and maintain results in the long term. However, variability in antibiotic regimens is still a topic to be debated; either in primary or permanent dentitions, antibiotic resistance still needs to be better evaluated for these cases, and the use of surgical approachesis still needed in some cases/defects. In fact, the inclusion of host modulation therapies is also a desired future approach that deserves to be studied as an alternative to the ABX approach. Given the current classification [213], patients with early onset aggressive forms of periodontitis are now classified in the same risk grade as diabetics and smokers, and the disease in primary dentition, although clearly reported in the literature, is still not properly diagnosed and not mentioned in the new classification, possibly leaving pediatric dentists in a “vacuum” regarding periodontal disease diagnosis in children. Further studies certainly should include the unique clinical characteristics of this disease and specific inclusion criteria if we wish to specify unique features of this disease without confounding factors.

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8 | Conclusion

Based on this narrative review, it can be concluded that C-MIP is a unique disease carrying distinct clinical features and microbiological/immunological/susceptibility patterns from other forms of periodontitis. A higher disease prevalence is observed in populations of African descent, with usual onset under 30 years of age, along with very minimal gingival clinical inflammation and low biofilm accumulation (in the vast majority of cases). Despite the difficulties in the diagnosis of this disease in children, a rapid form of bone loss has been diagnosed in both primary and mixed dentitions. The lack of an early diagnosis of this disease at this stage *may* be associated with disease establishment and progression in the permanent dentition [3]. Thus, it is crucial to emphasize the relevance of early periodontal assessment during pediatric dental examination, including probing and careful radiographic assessment [19]. Clinicians should be aware of differentiating early exfoliation due to the disproportionate rate of bone loss due to a pathological process as compared to physiological exfoliation patterns, involving apical root resorption and permanent root formation during eruption stages [13, 214]. All these clinical signs, along with the probing examination, can provide an accurate C-MIP diagnosis in children in primary and mixed dentitions.

A. actinomycetemcomitans, especially JP2 clone (serotype b), has been recognized as the keystone pathogen for early onset periodontitis [39, 52–55], including unique virulence factors (e.g., CDT) that elicit a strong host response [74]. Literature has shown that JP2 is associated with loss of attachment over time in both dentitions and potentially increases the risk for the development of aggressive forms of periodontitis [85]. This pathogen has also been highly identified in primary dentition, and vertical transmission is one of the hypotheses for such early colonization [93–95]. Despite the major role played by *A. actinomycetemcomitans* in this disease, its synergy with other pathogens such as *S. parasanguinis* and *F. alocis* can worsen clinical parameters over time [41, 54, 91]. In addition, particularities in C-MIP microbiological composition in different populations worldwide provide evidence that other pathogens can also play a relevant role in this disease [37, 38]. Immunological impairments such as neutrophil hypo and hyperfunction activities [15, 16, 124] along with an increased inflammatory profile, even in healthy siblings [132, 133], are common features observed in C-MIP patients/families. Moreover, IgG has been one of the hallmark immunoglobulins in this disease even after treatment [146, 152], and it may be uniquely differentiated in different populations [135].

NST + ABX remains the best non-invasive initial approach to treating C-MIP in both primary and permanent dentitions. Studies have shown that this clinical approach yields excellent outcomes in both the short and long term [3, 59, 190, 194, 207]. Surgical intervention may still be needed in certain cases, and alternative approaches certainly need to be better evaluated regarding their long-term effectiveness. It is crucial to keep all C-MIP patients in periodontal supportive therapy due to their increased susceptibility to tissue breakdown. Although the current classification suggests the aggregation of aggressive forms of periodontitis with other confounding factors that may increase the risk of disease progression (e.g., smoking and diabetes) by grading [213], it is important for clinicians to practice critical thinking during diagnosis and treatment planning based on the patient's history of disease breakdown and risk for disease progression in order to provide a personalized approach for each case.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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