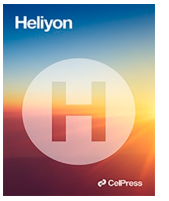
Heliyon 10 (2024) e26740

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Association of neutrophil defects with oral ulcers but undetermined role of neutrophils in recurrent aphthous stomatitis

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ARTICLE INFO

Keywords:
Neutrophils
Oral cavity
Oral ulcer
Recurrent aphthous stomatitis
Neutropenia
Extravasation
Respiratory burst

ABSTRACT

Objective: Recurrent oral ulcers and severe periodontal diseases in patients with quantitative or qualitative neutrophil defects highlight the important role of neutrophils in maintaining oral mucosal barrier homeostasis. Recurrent aphthous stomatitis (RAS) is a common oral mucosal disease affecting up to 25% of the population, yet its etiopathogenesis remains unclear, and management is unsatisfactory. This review aims to gain insight into the pathogenesis of RAS.
Design: This narrative review examines the characteristics of oral and blood neutrophils, the associations between neutrophil defects and the occurrence of oral ulcers, and the evidence for the involvement of neutrophils in RAS. To conduct the review, relevant literature was searched in PubMed and Google Scholar, which was then thoroughly reviewed and critically appraised.
Results: Neutropenia, specifically a decrease in the number of oral neutrophils, impaired extravasation, and defective ROS production appear to be associated with oral ulcers, while defects in granule enzymes or NETosis are unlikely to have a link to oral ulcers. The review of the histopathology of RAS shows that neutrophils are concentrated in the denuded area but are latecomers to the scene and early leavers. However, the evidence for the involvement of neutrophils in the pathogenesis of RAS is inconsistent, leading to the proposal of two different scenarios involving either impaired or hyperactive neutrophils in the pathogenesis of RAS.

1. Introduction

The oral cavity serves as a gateway for pathogens that infect the respiratory and gastrointestinal tracts. Moreover, the oral cavity is home to one of the most complex microbial communities in the human body, colonizing the mucosal and tooth surfaces [1]. However, the oral cavity remains inflammation-free, and healthy individuals are rarely infected by members of the oral microbiome. These observations suggest the presence of homeostatic host-microbial interaction in a steady state, where both innate and adaptive immune cells, along with salivary antimicrobial components and epithelial barrier, orchestrate the homeostatic oral mucosal barrier. Perturbation in salivary secretion, innate or adaptive immunity, leads to predisposition to diverse oral manifestations, including aphthous ulcers, oral infections by fungus or virus, and severe periodontal diseases [2–4].

Neutrophils are the most abundant (40–60%) leukocytes in the blood, and are responsible for phagocytosing and eliminating extracellular bacteria and fungi [5]. Neutrophils are rapidly recruited from the blood to tissues in response to infection or tissue damage but are scarcely found in tissues outside the vasculature under normal circumstances. However, the gingiva uniquely recruits neutrophils even in germ-free mice. Furthermore, the junctional epithelium located at the gingiva provides a specialized route through

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https://doi.org/10.1016/j.heliyon.2024.e26740
Received 21 June 2023; Received in revised form 17 February 2024; Accepted 19 February 2024
Available online 22 February 2024

which neutrophils migrate to the gingival sulcus and ultimately enter the oral cavity [6]. Defects in neutrophil number or function can result in recurrent infections with extracellular pathogens. Patients with quantitative or qualitative neutrophil defects often experience recurrent oral ulcers and severe gingivitis/periodontitis, underscoring the significance of neutrophils as an integral component of the homeostatic oral mucosal barrier [4].

Recurrent aphthous stomatitis (RAS) is one of the most prevalent oral mucosal diseases and may affect up to 25% of the population [7,8]. RAS is characterized by the recurrent occurrence of one or multiple shallow ulcers, which are circular to oval shape and very painful, taking longer to heal than non-specific ulcers. RAS is classified clinically into three categories: minor (8–10 mm in size), major (>10 mm in size), and herpetiform (multiple ulcers of 2–3 mm in size). Minor and herpetiform ulcers typically heal within 10–14 days without scarring, but major RAS ulcers can persist for up to six weeks and may result in scarring [9]. Despite its high prevalence, the etiopathogenesis of RAS remains unclear, and its management also remains unsatisfactory. RAS can also occur as a symptom of rare systemic diseases, including inflammatory bowel disease, systemic lupus erythematosus, celiac disease, periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome, and Behçet's disease [9]. Particularly, PFAPA syndrome and Behçet's disease share genetic susceptibility loci with RAS, suggesting common pathogenic mechanisms [10]. Interestingly, accumulated literature reports neutrophil hyperactivity in Behçet's disease patients [11], introducing complexity to our understanding of neutrophil involvement in RAS.

This review article aims to gain insight into the pathogenesis of RAS by dissecting the neutrophil defects associated with oral ulcer occurrence. To achieve this aim, this review article will first compare oral neutrophil characteristics with those of blood neutrophils; second, examine neutrophil count or function deficiencies associated with oral ulcer occurrence; and third, analyze evidence supporting the involvement of neutrophils in RAS pathogenesis. Finally, this review proposes two different scenarios involving neutrophils in the pathogenesis of RAS and suggests critical questions to clarify the role of neutrophils in RAS. While the second section compares the effects of defective neutrophil components on gingivitis/periodontitis and oral ulcers, this review article does not focus on gingivitis/periodontitis.

2. Characteristics of oral neutrophils

2.1. Oral neutrophil counts

Neutrophils exhibit a circadian rhythm of recruitment to the oral cavity, with the recruitment rate being lowest early in the morning (approximately 30,000 per minute in young adults with good oral health), increasing 4–5 fold during the day, and decreasing during the night [12]. Two studies have shown an increase in oral neutrophil count during experimental gingivitis [12,13]. Interestingly, one-third of the subjects in both studies presented an exaggerated influx of oral neutrophils. Moreover, the group with the exaggerated neutrophil influx experienced higher levels of inflammation, as evidenced by increased bleeding on probing and mean pocket depth, than the group with the low oral neutrophil influx [13]. Cross-sectional studies have reported increased oral neutrophil counts in patients with gingivitis or periodontitis, with positive correlations observed between the oral neutrophil count and measures of periodontal disease severity, gingival bleeding, or pocket depth [14–16]. Notably, the oral neutrophil counts have no correlation with the numbers of blood neutrophils in patients with periodontal diseases [15]. However, oral neutrophil counts well reflect blood neutrophil counts in individuals with neutropenia or those recovering from neutropenia [17–19].

2.2. Migration routes

It is believed that most oral neutrophils enter the oral cavity through the gingival crevice, as edentulous individuals have substantially lower oral neutrophil counts compared with dentate subjects [19,20]. Recently, transepithelial channels for leukocytes have been characterized in the gingival junctional epithelium of mice, which provide expressways from the lamina propria to the bottom of the gingival sulcus without interruption by the basement membrane or keratinocytes [21].

However, the source of oral neutrophils detected in edentulous individuals is not clear. While the recruitment of neutrophils into the salivary glands in the steady state is controversial [22,23], a study has shown that the neonatal oral (buccal) epithelium transiently recruits neutrophils in a microbiota- and IL-17-dependent manner in mice, which disappear after weaning (4 weeks old) with the maturation of the oral mucosa. The neonatal oral epithelium has increased permeability with low levels of junctional proteins, and the authors propose that the recruited neutrophils provide important protection against a high microbial load during the neonatal period [24]. If the neonatal oral epithelium is permeable and recruits neutrophils in humans as well, there is a possibility that neutrophils may migrate through the oral epithelium before tooth eruption. Although neutrophils are rarely seen by microscopy in normal skin, a parabiosis approach using neutrophil-specific reporter mice and Fucosyltransferase 7-deficient mice revealed that neutrophils actively infiltrate most healthy tissues, including the skin [25], implying the possibility of neutrophil recruitment to oral mucosa in steady state. Notably, neutrophils are mostly localized outside the blood vessels in the intestine and spleen, but mostly intravascularly in the lung and liver [25]. A human oral mucosa cell atlas using a single-cell RNA-seq approach and flow cytometry reported the presence of a neutrophil population in healthy buccal mucosa, but whether the neutrophils are located extravascularly or intravascularly is not known [26]. Importantly, direct evidence for the presence of neutrophils in or transmigration through the oral epithelium other than the junctional epithelium in steady state is not yet available.

2.3. Phenotypic characteristics

Several studies have demonstrated that oral neutrophils exhibit an activated phenotype compared to blood neutrophils. Transmission electron microscopy of oral neutrophils reveals a lighter electron-lucent cytoplasm, indicating translocation of cytosolic components to the cell membrane, which is a phenotype of stimulated neutrophils. Additionally, phagosomes containing bacteria are commonly observed in oral neutrophils, but not in blood neutrophils. Oral neutrophils have decreased mean numbers of granules per unit area of cytoplasm, indicating degranulation of a portion of granules [17,27]. Cell surface marker expression examined by flow cytometry supports the degranulated and activated status of oral neutrophils (Fig. 1). They have upregulated levels of CD63, CD66, and CD11b, the degranulation markers [15,16]. Conversely, surface molecules involved in adhesion to endothelial cells, diapedesis, and chemotaxis are detected at decreased levels in oral neutrophils [28–37]. In addition, oral neutrophils express decreased levels of CD16, CD43, CD50, and CD162 that are shed upon activation [28–30,38,39].

In line with the activated phenotype, oral neutrophils produce reactive oxygen species (ROS), including superoxide (O_2^-), without any stimulation [15,40], which decreases with time after isolation from the oral cavity [40]. Furthermore, neutrophil extracellular trap (NET) formation is observed in oral neutrophils without stimulation [41].

Collectively, oral neutrophils are thought to be activated by bacteria they encounter during emigration or in the oral cavity, and their morphologic characteristics are simulated by *in vitro* incubation of blood neutrophils with *Streptococcus oralis* [27]. This activated phenotype of oral neutrophils is exaggerated in patients with chronic periodontitis [16,27]. To denote the activated status of oral neutrophils, Fine et al. defined the oral neutrophils from healthy individuals and periodontitis patients as "parainflammatory" and "proinflammatory", respectively [16]. The parainflammatory neutrophils interact with commensal bacteria without inducing inflammation and exhibit intermediate levels of activation between resting and proinflammatory neutrophils.

Despite their activated phenotype, oral neutrophils maintain the ability to phagocytose microbes and produce additional ROS [15,16,40,41]. They exhibit increased phagocytic capacities for various oral bacteria compared to blood neutrophils but present a limited killing ability for phagocytosed *Escherichia coli* [41]. The enhanced phagocytic capacity may be attributed to the increased levels of CD11b, CD66b, and CD63, which increase the adhesive activity of CD11b/CD18 (CR3), involving phagocytosis [42–44]. Although oral neutrophils produced higher levels of superoxide and ROS in response to phorbol 12-myristate 13-acetate (PMA) and *Fusobacterium nucleatum*, respectively, than blood neutrophils [15,40], they do not exhibit a chemotactic response or ROS production in response to N-formyl-met-leu-phe (fMLP) [40,41]. The impaired response to fMLP of oral neutrophils is explained by low levels of fMLP receptor expression [41], and oral neutrophils regained reactivity to fMLP when their endogenous ROS production decreases over time [40]. This suggests that the functional capacity of oral neutrophils may vary depending on their activation status and changes in the expression levels of diverse surface receptors.

3. DEFECTS in neutrophil counts or function and involvement of oral ulcers as clinical manifestations

3.1. Neutropenia

Neutropenia is a condition where the absolute neutrophil count (ANC) in the blood falls below 1500/μl. The neutropenia is classified as mild (1000–1500), moderate (500–1000), or severe (<500), depending on the ANC. In addition, neutropenia can be chronic (persists for more than 3 months), intermittent, and cyclic (occurs in a 21-day interval), depending on the duration.

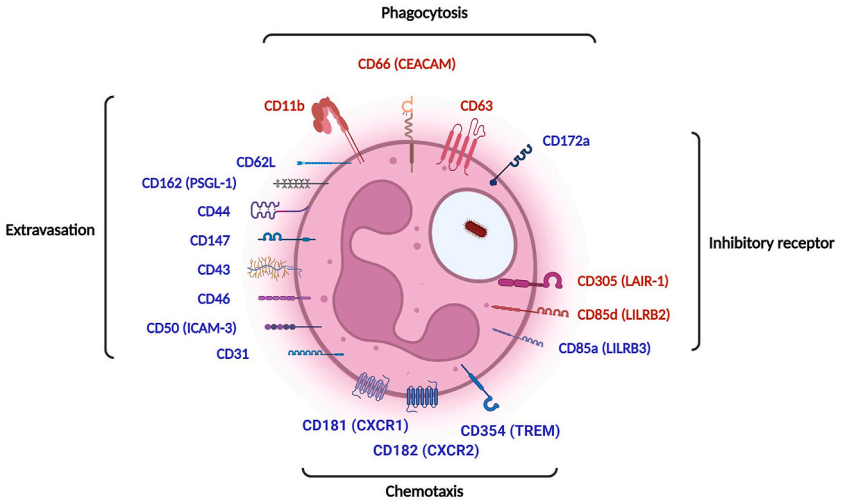

Fig. 1. Surface molecules expressed on oral neutrophils. Letters in red color indicate the molecules that are upregulated compared to blood neutrophils, while letters in blue color represent the downregulated molecules. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
The involvement of oral manifestations in congenital immunodeficiencies that affect the number or function of neutrophils.

Subgroup	Disease	Gene mutated	OMIM code	Defects[b] and Characteristics of Neutrophils	Oral Ulcers	Gingivitis/ Periodontitis	References
Neutropenia	SCN			Chronic SN	Recurrent, painful	Early onset AgP	[53,54]
		ELANE	202700		77%	62%	[55,56]
		HAX1[a]	202700				[57,58]
		JAGN1[a]	616022	Decreased granules			[59]
		CSF3R	202700				[60]
		SEC61A1	609213				[61]
		SRP54	604857				[62]
		SRP68	604858				[63]
		TCIRG1[a]	202700				[64]
	X-linked SCN	*WAS*	301000	Chronic SN but normal oNeutrophil count Increased chemotaxis to chemokines Increased phagocytosis of bacteria	No	No	[65,66]
	Cyclic neutropenia	*ELANE*	162800	SN for 3–5 days with a 21-day periodicity	Recurrent (93%)	Early onset AgP (35%)	[56,67]
	Barth syndrome	*TAZ*[a]	302060	Variable degree of N, chronic/intermittent	Persistent	Gingivitis	[68,69]
	Glycogen storage disease type Ib	*SLC37A4*[a]	232220	Chronic neutropenia, absent to severe Defective ROS production & chemotaxis	Recurrent (69%[c])	Gingivitis (69%[c])	[70,71]
	Cohen Syndrome (>200 cases)	*VPS13B*[a]	216550	Intermittent neutropenia, mild to moderate	Recurrent	Gingivitis	[72–74]
	Poilkiloderma with neutropenia	*USB1*[a]	604173	Neutropenia, mild to severe	No report	No report	[75–79]
	Wolcott-Rallison syndrome	*EIF2AK3*	226980	Neutropenia, absent to mild	No report	No report	[80]
Migration Defect	LAD				Persistent ulcers	Early onset AgP	[3]
	Type I (>320 cases)	*ITGB2*	116920	Defects in firm adhesion & chemotaxis	24%–52%[c]		[81,82]
	Type II (<20 cases)	*SLC35C1*	266265	Defects in rolling adhesion & chemotaxis			[83,84]
	Type III (<40 cases)	*FERMT3*	612840	Defects in integrin activation & chemotaxis			[85,86]
	WDR1 deficiency (11 cases)		604734	Defects in chemokinesis & chemotaxis Normal bactericidal activity Normal ROS production	Severe ulcers leading to oral stenosis	No	[87–89]
Granule Defect	PLS (~250 cases)	*CTSC*[a]	245000	No NET formation, reduced chemotaxis Increased ROS production No defect in killing common bacteria	Stomatitis in some but no ulcer	Early onset AgP most patients	[90,91]
	CHS (<500 cases)	*LYST*[a]	214500	Giant azurophilic granules Neutropenia Delayed bactericidal activity & Impaired chemotaxis Normal ROS production	14.3%	81%	[92–94]
	SGD (<20 cases)	*CEBPE*	245480	Lack specific granules Defect in chemotaxis to chemokines Defect in bactericidal activity Normal O_2^- but reduced •OH production	No	No	[95–98]
Respiration	CGD			No ROS production, defect in NETosis	Recurrent	Gingivitis but no AgP	[99–104]

(*continued on next page*)

Table 1 (*continued*)

Subgroup	Disease	Gene mutated	OMIM code	Defects[b] and Characteristics of Neutrophils	Oral Ulcers	Gingivitis/ Periodontitis	References
Burst Defect		*CYBB*	306400		5%–26%	11%–35%	
		CYBA	233690				
		NCF1	233700				
		NCF2	233710				
		NCF4	613960				

SCN: severe congenital neutropenia; SN: sever neutropenia; AgP: aggressive periodontitis; oNeutrophil: oral neutrophil; ROS: reactive oxygen species; LAD: leukocyte adhesion deficiency; PLS: Papillon-Lefèvre syndrome; NET: neutrophil extracellular trap; CHS: Chediak-Higashi syndrome; SGD: neutrophil specific granule deficiency; CGD: chronic granulomatous disease.

[a] Genetic defects that also affect non-hematologic compartments.

[b] The term "Defect" or "Defective" was used when the value is less than 50% of normal. Otherwise, "decreased" is used.

[c] The prevalence of oral infections, including oral ulcers and periodontal diseases.

Neutropenia has a diverse etiology that can be divided into acquired and congenital [45].

Acquired neutropenia with clinical sequelae can be caused by infection, autoimmune diseases, malignancies involving the bone marrow, nutrition deficiency, and exposure to drugs [45,46]. Autoimmune neutropenia can occur as a primary or secondary manifestation of other autoimmune diseases, such as autoimmune thrombocytopenia, systemic lupus erythematosus, or autoimmune lymphoproliferative syndrome [47,48]. In primary autoimmune neutropenia, patients are usually asymptomatic, but oral inflammation may occur occasionally [45,49]. Recurrent oral aphthae have been reported as the first symptom of autoimmune lymphoproliferative syndrome [48]. Among the acquired neutropenia, drug-induced neutropenia is the most common. Besides chemotherapeutic drugs that suppress the bone marrow, various medications can cause idiosyncratic agranulocytosis [46,50]. Erythematous and ulcerative inflammation of the oral mucosa, called "oral mucositis", is one of the most frequent complications of chemotherapy. Although its occurrence is associated with diverse factors, such as the dosage and duration of chemotherapy, the treatment stage, and herpes simplex virus type 1 activation, the severity and duration of neutropenia are strongly associated with the development of oral mucositis [51,52]. Oral mucositis typically develops at the time of neutropenic nadir but quickly heals once the ANC is recovered.

Congenital neutropenia (CN) is a group of neutropenic disorders caused by inborn genetic defects. These disorders can be chronic, intermittent, or cyclic and vary in severity. Although CN is an extremely rare condition, it has been well characterized. To date, over 30 genes have been identified as causing CN [45,53,54]. Mutations in these genes may also lead to other hematologic and extra-hematologic abnormalities. Thus, neutropenia can be presented as one of the phenotypes of syndromic diseases [53]. To understand the role of neutrophils in oral ulcers, only CNs without other hematologic defects are listed in Table 1 [53–104]. The detailed molecular pathogenesis of CNs is beyond the scope of this review and can be found in other reviews [53,54].

Patients with severe congenital neutropenia (SCN) are at a high risk of developing infections from the neonatal period, and the disease is typically diagnosed in early childhood. Recurrent and painful aphthous stomatitis, severe gingivitis, and early onset aggressive periodontitis are frequently observed in SCN patients [45,53,54]. Importantly, the presence of stomatitis or gingivitis is one of six diagnostic factors that predict CN in children [105].

Among all CN-linked genes, the ELANE mutation is the most prevalent (~45%) and can cause both SCN and cyclic neutropenia [54]. Unlike other CN-linked genes, ELANE mutation only affects the neutrophil compartment, making it a good model to study the role of neutropenia in infections. Patients with cyclic neutropenia have a lower risk of life-threatening infections compared to ELANE-SCN patients [56]. However, there is no significant difference in the risk of oral infections between SCN and cyclic neutropenia patients. According to a recent study of 143 patients with ELANE-related neutropenia, about 67% and 90% of patients experienced at least one episode of oral infections, respectively. Oral ulcers represented 77% and 93% of total distinct episodes, while gingivitis represented 62% and 35% of total distinct episodes in patients with SCN and cyclic neutropenia, respectively [56].

As the number of neutrophils at the infection site is the most important factor associated with infection risk, the degree of neutropenia does not linearly translate to infection risk *in vivo* [54]. It is worth mentioning X-linked SCN caused by a gain-of-function mutation in the Wiskott-Aldrich syndrome protein (WASp) as a unique case in this aspect. Despite having SCN, X-linked SCN patients are generally not at high risk of infections, and many are diagnosed as adults. Furthermore, oral ulcer and gingivitis have not been reported in these patients [66,106,107]. A gain-of-function mutation in WASp renders constitutive activation of WASp, leading to a hyperactive phenotype of neutrophils with increased chemotaxis and phagocytic abilities [66]. Notably, normal numbers of neutrophils in saliva are reported in X-linked SCN patients, and mouse models harboring the corresponding human mutations show an increased number of neutrophils at infection sites accompanied by an increased neutrophil migration ability [66].

In syndromic diseases accompanying neutropenia, neutropenia can manifest in various forms. In Barth syndrome, neutropenia can be severe and chronic, cyclic, or intermittent and unpredictable. Nadirs in the ANC are associated with bacterial infection, including oral ulcers and gingivitis [68,69]. Glycogen storage disease type Ib is a rare genetic metabolic disorder characterized by hypoglycemia and excessive glycogen accumulation in the liver [70]. In addition to metabolic symptoms, patients suffer from a variable degree of neutropenia and neutrophil dysfunction, leading to recurrent infections. A recent review of 103 patients reported that 69% of patients had a history of recurrent mouth ulcers and gingivitis [71]. In Cohen syndrome, mild to moderate neutropenia is a common feature of disease, together with craniofacial, ocular, and limb anomalies, infantile hypotonia, and developmental delay [72]. Some patients

experience recurrent infections, recurrent oral ulcers, or gingivitis, but no severe infections [73,74]. Poikiloderma with neutropenia is a very rare genetic disorder characterized by poikiloderma, pachyonychia, and chronic neutropenia. Patients may present with mild to severe neutropenia and increased susceptibility to infections such as pulmonary infections, otitis, and sinusitis, but oral infection has not been reported in these patients [76–79]. Currently, it is unknown whether a normal number of neutrophils migrate to the oral cavity despite severe neutropenia in these patients.

3.2. Defects in motility

The recruitment process of neutrophils to infection sites can be divided into two main stages: extravasation and migration along the chemokine gradients within the extravascular space. Extravasation also involves multiple sequential steps, including rolling adhesion, firm adhesion, crawling, and transendothelial migration [5]. All these steps of neutrophil recruitment depend on the dynamic remodeling of the actin cytoskeleton [5].

Leukocyte adhesion deficiency (LAD) is a group of rare genetic disorders that cause defects in the adhesion of neutrophils to endothelial cells and subsequent extravasation. Three causative genes have been identified, affecting different steps of neutrophil-endothelial cell interaction: *SLC35C1* in LAD-II for rolling adhesion between selectin ligands and E− or P-selectins, *FERMT3* in LAD-III for integrin activation required for firm adhesion, and *ITGB2* in LAD-I for firm adhesion between integrins and ICAMs [81–86]. The neutrophils of all LAD subtypes also present a defect in chemotaxis [108]. Recurrent infections of the skin and mucosal surfaces, which can be life-threatening, are shared by all subtypes, and painful oral ulcers and aggressive periodontitis during childhood are persistent clinical symptoms [84,86,108]. Particularly, severe periodontitis is the only persistent clinical symptom in LAD-II where the infection severity is milder than that in LAD-I [84]. A comprehensive review of all LAD-I cases published between 1975 and 2017 found that oral infections, including periodontitis and oral ulcers, are reported in 24% of severe LAD-I (CD18 expression on neutrophils<2%) and 52% of moderate LAD-I (CD18 expression on neutrophils>2%) [82]. The absence of neutrophils in tissue delays wound healing, which is caused by increased production of IL-23 by macrophages and excessive recruitment of Th17 cells [109]. Notably, inhibition of excessive IL-23 by ustekinumab has been reported to resolve inflammatory lesions in two LAD-I patients with non-healing skin ulcers, periodontitis, and oral ulcers [110,111].

Genetic defects that severely impair neutrophil motility, both random (chemokinesis) and directed (chemotaxis), have been recently identified in the *WDR1* gene. The *WDR1* gene encodes WD repeat–containing protein 1 (WDR1, also called actin-interacting protein 1) that regulates actin filament disassembly, a crucial part of actin-cytoskeleton-remodeling [112]. WDR1-mutated neutrophils also exhibit characteristic abnormal morphology with nuclear herniation, but they retain their normal abilities to kill bacteria and produce ROS [87]. WDR1 deficiency also affects the lymphoid compartment, resulting in B-cell lymphopenia, a lack of switched memory B cells, and aberrant T-cell activation [89]. Moreover, accumulated F-actin in WDR1-deficient cells can activate the pyrin inflammasome, leading to an autoinflammatory phenotype [88]. Patients with WDR1 deficiency exhibit recurrent infections and severe aphthous stomatitis leading to oral stenosis, but they do not suffer from severe periodontitis [87–89].

3.3. Defects in granule proteins

Papillon-Lefèvre syndrome (PLS) is a rare genetic disorder characterized by keratosis palmoplantaris and severe prepubertal periodontitis [90]. PLS is caused by mutations in the *CTSC* gene, which encodes cathepsin C, a protein that is abundantly expressed in neutrophils, lymphocytes, and keratinocytes [90]. In neutrophils, cathepsin C is required for the activation of many granule-associated serine proteases, including cathepsin G, proteinase 3, and neutrophil elastase, as well as an antimicrobial peptide LL37, which are important for antimicrobial defence. The *CTSC* mutations lead to complete degradation of granule serine proteases in mature neutrophils [113,114]. Despite the lack of serine proteases in the neutrophils of PLS patients, their ability to kill common bacteria, such as *Klepsiella pneumoniae*, *E. coli*, and *Staphylococcus aureus*, is not impaired [115]. Furthermore, PLS neutrophils have a severe defect in the formation of neutrophil extracellular traps (NETs) as well as a decreased ability to migrate toward chemokines (fMLP and CCL-3), but an increased ability to produce ROS and inflammatory cytokines [91]. While systemic immunodeficiency in PLS is relatively mild, with only 15–20% of patients predisposed to recurrent infections, local periodontitis is profoundly aggressive [115]. Interestingly, patients with PLS may have erythematous oral mucosa after tooth eruption, but no oral ulcers have been reported [116].

Chediak-Higashi syndrome (CHS) is a rare genetic disorder characterized by partial oculocutaneous albinism, mild coagulation defect, an increased susceptibility to infections, and neurological deficits [92]. CHS is caused by mutations in the *LYST* gene that encodes a lysosomal trafficking regulator protein, which lead to enlarged lysosomes and abnormal lysosome-related organelles in melanocytes, platelets, neutrophils, NK cells, cytotoxic T lymphocytes, and neurons. In particular, the giant azurophilic granules present in neutrophils affect bactericidal activity and chemotaxis function. CHS patients may also exhibit neutropenia [93]. A recent systematic review of 21 CHS cases (mean age 15.9 ± 8.8 years) published in 14 articles reported gingivitis/periodontitis as the most common oral manifestation, affecting 81% of patients. The prevalence of oral ulcers was 14.3% [94].

Neutrophil-specific granule deficiency (SGD) is an extremely rare genetic disorder characterized by the infantile onset of recurrent pyogenic infections and neutrophils lacking specific granules. It is caused by congenital defects in transcription factor CCAAT/enhancer binding protein Epsilon [95]. The neutrophils in SGD patients present defects in chemotaxis and bactericidal activity, but their ability to produce ROS is mostly preserved [96–99]. Recurrent infections frequently involve the skin, ears, lung, and lymph nodes, but neither oral ulcers nor periodontal diseases have been reported as clinical manifestations in patients [95–99].

3.4. Defects in the respiratory Burst

Neutrophils arrived at infection sites perform antimicrobial effector functions through phagocytosis, degranulation, and NET formation. Phagocytosed microbes are killed by (i) the antimicrobial contents of primary and secondary granules fused with the phagosome and (ii) ROS produced by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which are then pumped into the phagocytic vacuole [5].

The importance of NADPH oxidase in microbial killing is evident in chronic granulomatous disease (CGD), which is caused by a lack or dysfunction of this enzyme [99]. NADPH oxidase is composed of the core cytochrome *b*558 subunits (p91phox and p22 phox) and cytoplasmic components (p47 phox, p65 phox, p40 phox, and Rac). A defect in any of the five phox proteins results in defective ROS production and the development of CGD [99]. CGD is characterized by severe and recurrent bacterial and/or fungal infections that mostly affect the lungs, skin, lymph nodes, gastrointestinal tract, and liver [99]. Recurrent oral ulcers have been observed in 5%–23% of CGD patients in multiple cohorts: 5% of 130 patients in China, 11% of 63 patients in Turkey, 11% of 429 European patients, and 23% of 39 patients in Germany [99–102]. Some studies have reported gingivitis, with 11% of 429 European patients having gingivitis/caries and 35% of 60 Italian patients having stomatogingivitis [103,104]. However, there is no evidence that CGD patients are susceptible to periodontitis [117]. Of note, carriers of the X-linked CGD gene *CYBB* mutation have two populations of phagocytes in the peripheral blood, one normal and one with defective ROS production [118]. Interestingly, carriers of X-linked CGD are not susceptible to infection but often suffer from RAS [119,120]. Kragballe et al. reported significantly lower ROS production by neutrophils from X-linked CGD carriers with RAS (n = 10) than those from symptom-free carriers (n = 5) [120].

3.5. Summary

Based on the review of conditions associated with impaired neutrophil counts or function, it appears that neutropenia, specifically a decrease in the number of oral neutrophils, impaired extravasation, and defective ROS production are associated with oral ulcers. However, there does not seem to be a link between defects in either granule enzymes or NETosis and the occurrence of oral ulcers.

4. Evidence for involvement of neutrophils in the pathogenesis of RAS

4.1. Where are neutrophils observed in RAS lesions?

Histopathologic investigation of RAS ulcers is relatively limited as biopsy is not a routine component of RAS management. However, an excellent report exists on the pathologic features of RAS lesions from premonitory and preulcerative stages to healing stage [121]. In the premonitory and preulcerative stages, an inflammatory focus of mononuclear (lymphoid) cells is observed in the lamina propria. Edematous and degenerative changes are also seen in the basal and lower prickle layers of the epithelium above the inflammatory focus, with a few infiltrated inflammatory cells [121]. Transmission electron microscopy has shown the presence of apoptotic prickle cells and increased intraepithelial lymphocytes and monocytes adjacent to the apoptotic cells [122,123]. A few neutrophils have also been noted adjacent to the apoptotic prickle cells [122,124].

In the ulcerative stage, neutrophils are confined to the breach within the epithelium and the fibrinous clot at the surface of the ulcer initially, but gradually spread to adjacent and subjacent tissues, where mononuclear cells predominate [121]. The number of neutrophils at the ulcer beds reaches that of lymphocytes, but lymphocytes always outnumber neutrophils in areas adjacent to the ulcer margins [124]. In the early lesions of RAS (within 24 h of ulcer onset), perivascular mononuclear infiltration consisting of lymphocytes, monocytes, and some mast cells reflects the dominance of mononuclear cell infiltration, and perivascular neutrophils are observed at the border of 2-day-old ulcers [123,125].

The histology of non-specific ulcers without recurrent history is characterized by less marked mononuclear and perivascular

Table 2
Studies on peripheral blood cell parameters in RAS patients.

Study	Subjects	WBC	ANC	ALC	APC	NLR	PLR	MPV	SII
Ueta et al., 1993 [129]	40 aRAS vs. 20 Con	N.R.	↓	↑	N.R.	N.R.	N.R.	N.R.	N.R.
	40 rRAS vs. 20 Con	N.R.	≈	≈	N.R.	N.R.	N.R.	N.R.	N.R.
Terzi et al., 2016 [130]	80 aRAS vs. 0 Con	↑	↑	≈	≈	↑	≈	≈	N.R.
Uluyol et al., 2017 [131]	19 aRAS vs. 40 Con	N.R.	N.R.	N.R.	N.R.	↑	N.R.	↑	N.R.
	42 iRAS vs. 40 Con	N.R.	N.R.	N.R.	N.R.	≈	N.R.	≈	N.R.
Kayabasi et al., 2019 [132]	39 aRAS vs. 60 Con	↑	N.R.	N.R.	N.R.	↑	≈	≈	N.R.
	33 iRAS vs. 60 Con	↑	N.R.	N.R.	N.R.	↑	≈	≈	N.R.
Karaer, 2020 [133]	137 aRAS vs. 137 Con	≈	≈	≈	≈	≈	≈	≈	N.R.
Turan et al., 2021 [134]	97 aRAS vs. 90 Con	N.R.	≈	≈	≈	≈	≈	≈	N.R.
Atalay et al., 2022 [135]	97 aRAS vs. 97 Con	N.R.	N.R.	N.R.	N.R.	↑	↑	N.R.	↑

WBC: white blood cell; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; APC: absolute platelet count; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MPV: mean platelet volume; SII: systemic immune inflammation index (=APCxANC/ALC); aRAS: active recurrent aphthous stomatitis; iRAS: inactive recurrent aphthous stomatitis; rRAS: active recurrent aphthous stomatitis re-examined after remission; Con: control; N.R.: not reported.

infiltration and more pronounced neutrophil infiltration compared with RAS [123]. The lymphoid cells observed in RAS are predominantly T cells, but reports on the proportion of $CD4^+$ and $CD8^+$ T cells are not consistent [126–128]. After the expansion of lesions stops, the number of neutrophils decreases in the adjacent tissues remote from the ulceration, and neutrophils predominate only at the top of the lesion at the healing stage [121]. Therefore, neutrophils are latecomers to the scene but early leavers and concentrated in the denuded area.

4.2. Is RAS associated with changes in neutrophil counts?

Several groups investigated peripheral blood cell parameters to determine if excessive systemic inflammation is associated with the pathogenesis of RAS as summarized in Table 2 [129–135]. Most studies have focused on the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV), which are widely used as systemic inflammatory indices in various inflammatory conditions [136–138].

Of seven studies, only two included inactive RAS patients, and only one of these reported a significant increase in NLR in inactive RAS patients compared with control subjects, with no differences in PLR and MPV between the groups [131,132]. When comparing active RAS patients and control subjects, four of six studies reported a significant increase in NLR in RAS [130–132,135]. In most studies that reported PLR and MPV, these indices did not differ between the two groups [130–135]. Furthermore, only one of four studies reported an increase in the ANC in active RAS patients compared with controls, while one study reported a decrease (but not neutropenia) in ANC that was restored after remission [129,130]. Even in patients with SCN, ANC is often normal during infection [53]. These findings suggest that RAS is not associated with overt systemic inflammation, even during the active phase.

Unfortunately, no studies have investigated changes in oral neutrophil count. The presence of ulcerative lesions will result in an increase in the oral neutrophil counts. However, whether RAS patients experience a change in oral neutrophil counts during the premonitory/preulcerative phases will answer an important question regarding the role of oral neutrophils in the initiation of RAS. Considering the more pronounced neutrophil infiltration observed in non-specific ulcers compared with RAS [123], a comparison of oral neutrophil counts in non-specific ulcers and RAS may provide an insight into the different healing processes of the two entities.

4.3. Is RAS associated with changes in neutrophil functions?

Several studies have investigated various functions of blood or oral neutrophils obtained from RAS patients and control subjects (Table 3). Dagalis et al. reported no differences in chemokinesis and chemotaxis to fMLP of blood neutrophils obtained from patients with active RAS compared to those of a control group [139]. However, Sistig et al. reported about a 50% reduction in the chemokinesis ability of blood neutrophils from active RAS patients, which partly recovered after remission but remained low compared with that of controls [140]. Five groups investigated the ingestion ability of blood, oral, or both neutrophils in active RAS patients using various targets: opsonized sheep red blood cells (SRBC), opsonized Candida, non-opsonized yeast, or non-opsonized latex particles. While two

Table 3
Studies on neutrophil functions in RAS patients.

Study	Subjects	Neutrophil Functions Tested	Major Findings		
			aRAS vs. Con	rRAS vs. aRAS	rRAS vs. Con
Dagalis et al., 1987 [139]	22 RAS*, 22 Con	Chemokinesis, chemotaxis to fMLP by bNeutrophils	≈	N.E.	N.E.
Sistig et al., 2001 [140]	51 aRAS, 51 rRAS, 47 Con	Chemokinesis by bNeutrophils	↓	↑	↓
		Ingestion of opsonized SRBC by bNeutrophils	↓	≈	↓
		Intracellular killing of SRBC by bNeutrophils	≈	≈	↑
		Non-phagocytic lysis of SRBC by bNeutrophils	≈	↓	↓
Lukac et al., 2003 [141]	15 aRAS, 20 Con	Ingestion of non-opsonized yeast by oNeutrophils	↓	N.E.	N.E.
		Intracellular killing of yeast by oNeutrophils	≈	N.E.	N.E.
Altinor et al., 2003 [142]	48 aRAS, 22 Con	Ingestion of non-opsonized yeast by bNeutrophils	↑	N.E.	N.E.
Kumar et al., 2010 [143]	30 aRAS, 30 Con	Ingestion of opsonized *Candida* by bNeutrophils	≈	N.E.	N.E.
		Ingestion of opsonized *Candida* by oNeutrophils	≈	N.E.	N.E.
		Intracellular killing of *Candida* by bNeutrophils	↓	N.E.	N.E.
		Intracellular killing of *Candida* by oNeutrophils	↓	N.E.	N.E.
Ueta et al., 1993 [129]	40 aRAS, 40 rRAS, 20 Con	Ingestion of non-opsonized LP by bNeutrophils	≈	≈	≈
		SOP (OZ, PMA) by bNeutrophils	↓, ↓	≈, ↑	↓, ≈
Wray et al., 1991 [144]	10 aRAS, 10 Con	SOP (resting, PMA) by bNeutrophils	≈, ≈	N.E.	N.E.
Lewkowicz et al., 2003 [145]	20 aRAS, 16 rRAS, 19 Con	SOP (resting, fMLP, OZ, PMA) by bNeutrophils	↑, ≈, ≈, ≈	≈,≈, ≈, ≈	↑, ↑, ≈, ≈

aRAS: active recurrent aphthous stomatitis; rRAS: recurrent aphthous stomatitis after remission; Con: control; fMLP: N-formyl-met-leu-phe; bNeutrophils: blood neutrophils.
oNeutrophils: oral neutrophils; SRBC: sheep red blood cell; N.E.: not examined; LP: latex particle; SOP: superoxide production; OZ: opsonized zymosan; PMA: phorbol I2-myristate 13-acetate.

studies reported 27% and 47% reductions in the ingestion abilities of blood and oral neutrophils, respectively, two studies reported no difference, and one study reported an increased ingestion ability [129,140–143]. Importantly, the increased ingestion ability decreased after treatment with colchicine, which significantly shortened the recovery period [142]. Only one of three studies reported a significant decrease in the intracellular killing activity of both blood and oral neutrophils from active RAS patients [140.141,143]. The three studies that examined superoxide production by blood neutrophils in active RAS patients also reported inconsistent results: decreased production by stimulation with opsonized zymosan or PMA [129], no significant differences at rest and by PMA stimulation [144], and increased production at rest but no difference by stimulation with fMLP, opsonized zymosan, or PMA [145].

Overall, two studies reported no difference, two reported enhanced function, and four reported reduced function of neutrophils in RAS. Because different studies often used different assays to measure the same parameter, direct comparison of the results is not possible. To better understand the role of neutrophils in the pathogenesis of RAS, standardized assays should be used, and an adequate sample size and normal range for each assay should be determined.

5. Conclusion

The review of acquired or congenital neutropenia clearly demonstrates a strong association between the neutropenia and the occurrence of oral ulcers. Cyclic neutropenia, in particular, provides the best evidence for the crucial role of neutrophils in maintaining the health of the oral mucosa. Approximately 90% of patients with cyclic neutropenia experience aphthous ulcers as one of the typical clinical symptoms, together with fever, malaise, and cervical adenopathy, that appear right after the nadir of ANC and regularly recur

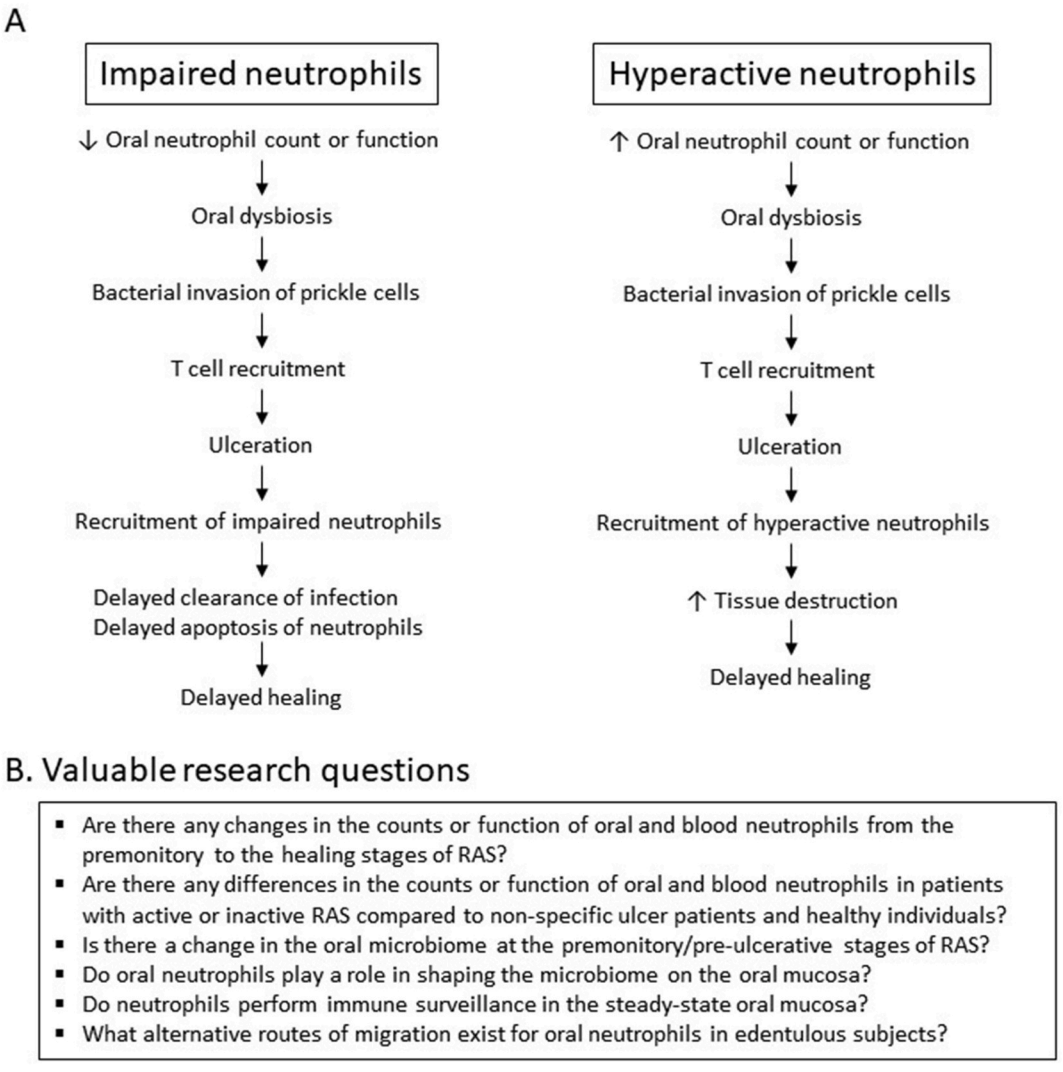

Fig. 2. Proposed models for the roles of neutrophils in the pathogenesis of recurrent aphthous stomatitis (RAS). (A) Two different models involving either impaired or hyperactive neutrophils are proposed. (B) Valuable research questions that will help to clarify the role of neutrophils in the pathogenesis of RAS are listed.

[146]. The absence of oral ulcers in patients with X-linked SCN indicates that the number of oral neutrophils, rather than blood neutrophils, is crucial [66]. In order for blood neutrophils to migrate to the oral cavity, extravasation is essential, which accounts for the oral ulcers observed in LAD and WDR1 deficiency (Table 1). The bactericidal activity of neutrophils consists of antimicrobial granule proteins and ROS. Interestingly, defects in ROS production, but not defects in granule proteins, are associated with oral ulcers (Table 1).

ROS not only kill the phagocytosed microbes but also themselves, inducing apoptosis in neutrophils. It is worth noting that phagocytosis of apoptotic neutrophils by nearby macrophages is important for switching the macrophage phenotype from pro-inflammatory to resolution phase and for the resolution of inflammation [147,148]. Moreover, the clearance of infection is another critical prerequisite for the resolution of inflammation [149].

The appearance of oral ulcers in various neutropenic patients after the nadir of ANC suggests that neutrophils have an immune surveillance function in the steady-state oral mucosa. Despite the fact that neutrophils actively infiltrate most healthy tissues in mice, neutrophils in the epithelium or lamina propria of healthy oral mucosa are rarely observed. Furthermore, RAS initiates with the recruitment of mononuclear cells, not that of neutrophils [121–123]. The susceptibility of oral bacteria to phagocytosis by neutrophils varies depending on the species [150]. Additionally, the ability of oral bacteria to invade oral keratinocytes also varies depending on the species and strains [151,152]. Oral neutrophils may provide a surveillance function by controlling the total load and invasive microbes in the oral microbiome. Whether or not neutrophils provide surveillance function in the oral mucosa or in the oral cavity, and how oral neutrophils shape the composition of the microbiome on the oral mucosa, are important questions to be answered.

The evidence for the involvement of neutrophils in the pathogenesis of RAS is inconsistent, and thus, it is not enough to draw a definitive conclusion. I propose two different scenarios that involve either impaired or hyperactive neutrophils in the pathogenesis of RAS (Fig. 2A). In the scenario involving impaired neutrophils, a decrease in the count or function of oral neutrophils at the premonitory stage may lead to oral dysbiosis, resulting in an increase in invasive microbes. The microbial invasion of epithelial cells may induce the degenerative changes in prickle cells and T cell recruitment observed at the pre-ulcerative stage. Microbe- and/or T-cell-mediated epithelial cell death induces ulceration. Neutrophils may be recruited finally by abundant N-formyl peptides released from extracellular bacteria that trespass through the ulcerated area [153]. The less pronounced neutrophil infiltration observed in RAS than in non-specific ulcers [123] or the impaired function of neutrophils may delay the clearance of infection or apoptosis of neutrophils, leading to delayed healing. In the scenario involving hyperactive neutrophils, the overall scenario is similar except that oral dysbiosis is induced by an increase in the number or function of oral neutrophils, and hyperactive neutrophils recruited to the ulcer beds cause excessive tissue destruction, leading to delayed healing. It is also possible that neutrophils have different roles in the premonitory and ulcerative/healing stages of RAS.

6. Limitations and future directions

The primary limitation of this review is the limited research on the role of neutrophils in rare systemic diseases associated with RAS. Currently, the observed neutrophil hyperactivity in Behçet's disease is considered a secondary response to an unidentified soluble factor present in the plasma of severely active patients, rather than a constitutive feature [11,154]. Additionally, the count or activation status of oral neutrophils in Behçet's disease has not been examined, warranting further investigation.

To evaluate the proposed roles of neutrophils in the pathogenesis of RAS, several questions can be addressed in studies using clinical samples.

1. Are there any changes in the counts or function of oral and blood neutrophils from the premonitory to the healing stages of RAS?
2. Are there any differences in the counts or function of oral and blood neutrophils in patients with active or inactive RAS compared to non-specific ulcer patients and healthy individuals?
3. Is there a change in the oral microbiome at the premonitory/pre-ulcerative stages of RAS?

Additionally, investigating whether oral neutrophils play a role in shaping the microbiome on the oral mucosa and perform immune surveillance in the steady-state oral mucosa would be scientifically significant questions to address (see Fig. 2B for an illustration).

Funding source

This study was supported by [the National Research Foundation of Korea (Daejun, Korea)] through the grants [2018R1A5A2024418 and 2020R1A2C2007038].

Statement

During the preparation of this work the author used ChatGPT (https://chat.openai.com/) in order to correct grammatical errors and improve readability. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

Youngnim Choi: Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT 3.5 in order to correct English. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Human Microbiome Project Consortium, Structure, function and diversity of the healthy human microbiome, Nature 486 (2012) 207–214, https://doi.org/10.1038/nature11234.
[2] A. Szczawinska-Poplonyk, K. Gerreth, A. Breborowicz, M. Borysewicz-Lewicka, Oral manifestations of primary immune deficiencies in children, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 108 (3) (2009) e9–e20, https://doi.org/10.1016/j.tripleo.2009.03.049.
[3] S. Jung, V. Gies, A.S. Korganow, A. Guffroy, Primary immunodeficiencies with defects in innate immunity: focus on orofacial manifestations, Front. Immunol. 11 (2020) 1065, https://doi.org/10.3389/fimmu.2020.01065.
[4] M.E. Peacock, R.M. Arce, C.W. Cutler, Periodontal and other oral manifestations of immunodeficiency diseases, Oral Dis. 23 (7) (2017) 866–888, https://doi.org/10.1111/odi.12584.
[5] P.X. Liew, P. Kubes, The neutrophil's role during health and disease, Physiol. Rev. 99 (2) (2019) 1223–1248, https://doi.org/10.1152/physrev.00012.2018.
[6] C. Zenobia, X.L. Luo, A. Hashim, T. Abe, L. Jin, Y. Chang, Z.C. Jin, J.X. Sun, G. Hajishengallis, M.A. Curtis, R.P. Darveau, Commensal bacteria-dependent select expression of CXCL2 contributes to periodontal tissue homeostasis, Cell Microbiol. 15 (8) (2013) 1419–1426, https://doi.org/10.1111/cmi.12127.
[7] J.A. Embil, R.G. Stephens, F.R. Manuel, Prevalence of recurrent herpes labialis and aphthous ulcers among young adults on six continents, Can. Med. Assoc. J. 113 (7) (1975) 627–630.
[8] R.B. Zain, Oral recurrent aphthous ulcers/stomatitis: prevalence in Malaysia and an epidemiological update, J. Oral Sci. 42 (1) (2000) 15–19, https://doi.org/10.2334/josnusd.42.15.
[9] C. Scully, S. Porter, Oral mucosal disease: recurrent aphthous stomatitis, Br. J. Oral Maxillofac. Surg. 46 (3) (2008) 198–206, https://doi.org/10.1016/j.bjoms.2007.07.201.
[10] K. Manthiram, What is PFAPA syndrome? Genetic clues about the pathogenesis, Curr. Opin. Rheumatol. 35 (6) (2023) 423–428, https://doi.org/10.1097/BOR.0000000000000956.
[11] S.F. Perazzio, L.E.C. Andrade, A.W.S. de Souza, Understanding behçet's disease in the context of innate immunity activation, Front. Immunol. 11 (2020) 586558, https://doi.org/10.3389/fimmu.2020.586558.
[12] C.R. Schiött, H. Löe, The origin and variation in number of leukocytes in the human saliva, J. Periodontal. Res. 5 (1) (1970) 36–41, https://doi.org/10.1111/j.1600-0765.1970.tb01835.x.
[13] N.C. Wellappuli, N. Fine, H.P. Lawrence, M. Goldberg, H.C. Tenenbaum, M. Glogauer, Oral and blood neutrophil activation states during experimental gingivitis, JDR Clinical and Translational Research 3 (1) (2018) 65–75, https://doi.org/10.1177/2380084417742120.
[14] M. Landzberg, H. Doering, G.M. Aboodi, H.C. Tenenbaum, M. Glogauer, Quantifying oral inflammatory load: oral neutrophil counts in periodontal health and disease, J. Periodontal. Res. 50 (3) (2015) 330–336, https://doi.org/10.1111/jre.12211.
[15] P. Rijkschroeff, I.D. Jansen, F.A. van der Weijden, B.J. Keijser, B.G. Loos, E.A. Nicu, Oral polymorphonuclear neutrophil characteristics in relation to oral health: a cross-sectional, observational clinical study, Int. J. Oral Sci. 8 (3) (2016) 191–198, https://doi.org/10.1038/ijos.2016.23.
[16] N. Fine, S. Hassanpour, A. Borenstein, C. Sima, M. Oveisi, J. Scholey, D. Cherney, M. Glogauer, Distinct oral neutrophil subsets define health and periodontal disease states, J. Dent. Res. 95 (8) (2016) 931–938, https://doi.org/10.1177/0022034516645564.
[17] D.G. Wright, A.I. Meierovics, J.M. Foxley, Assessing the delivery of neutrophils to tissues in neutropenia, Blood 67 (4) (1986) 1023–1030.
[18] G. Akpek, R.D. Knight, D.G. Wright, Use of oral mucosal neutrophil counts to detect the onset and resolution of profound neutropenia following high-dose myelosuppressive chemotherapy, Am. J. Hematol. 72 (1) (2003) 13–19, https://doi.org/10.1002/ajh.10250.
[19] R. Pink, J. Vondrakova, P. Tvrdy, P. Michl, J. Pazdera, E. Faber, I. Skoumalova, K. Indrak, Salivary Neutrophils Level as an Indicator of Bone Marrow Engraftment, vol. 153, Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia, 2009, pp. 263–269, https://doi.org/10.5507/bp.2009.051, 4.
[20] P. Rijkschroeff, B.G. Loos, E.A. Nicu, Impaired polymorphonuclear neutrophils in the oral cavity of edentulous individuals, Eur. J. Oral Sci. 125 (5) (2017) 371–378, https://doi.org/10.1111/eos.12367.
[21] C. Oh, H.J. Kim, H.M. Kim, Transepithelial channels for leukocytes in the junctional epithelium, J. Periodontal. Res. 57 (5) (2022) 1093–1100, https://doi.org/10.1111/jre.13043.
[22] J.J. Sharry, B. Krasse, Observations on the origin of salivary leucocytes, Acta Odontol. Scand. 18 (1960) 347–358, https://doi.org/10.3109/00016356009003017.
[23] M. Schapher, M. Koch, D. Weidner, M. Scholz, S. Wirtz, A. Mahajan, I. Herrmann, J. Singh, J. Knopf, M. Leppkes, C. Schauer, A. Grüneboom, C. Alexiou, G. Schett, H. Iro, L.E. Muñoz, M. Herrmann, Neutrophil extracellular traps promote the development and growth of human salivary stones, Cells 9 (9) (2020) 2139, https://doi.org/10.3390/cells9092139.
[24] N. Koren, K. Zubeidat, Y. Saba, Y. Horev, O. Barel, A. Wilharm, O. Heyman, S. Wald, L. Eli-Berchoer, H. Shapiro, C. Nadler, E. Elinav, A. Wilensky, I. Prinz, H. Bercovier, A.H. Hovav, Maturation of the neonatal oral mucosa involves unique epithelium-microbiota interactions, Cell Host Microbe 29 (2) (2021) 197–209.e5, https://doi.org/10.1016/j.chom.2020.12.006.
[25] M. Casanova-Acebes, J.A. Nicolás-Ávila, J.L. Li, S. García-Silva, A. Balachander, A. Rubio-Ponce, L.A. Weiss, J.M. Adrover, K. Burrows, N. A-González, I. Ballesteros, S. Devi, J.A. Quintana, G. Crainiciuc, M. Leiva, M. Gunzer, C. Weber, T. Nagasawa, O. Soehnlein, M. Merad, A. Hidalgo, Neutrophils instruct homeostatic and pathological states in naive tissues, J. Exp. Med. 215 (11) (2018) 2778–2795, https://doi.org/10.1084/jem.20181468.

[26] D.W. Williams, T. Greenwell-Wild, L. Brenchley, N. Dutzan, A. Overmiller, A.P. Sawaya, S. Webb, D. Martin, Nidcd/Nidcr Genomics and Computational Biology Core, G. Hajishengallis, K. Divaris, M. Morasso, M. Haniffa, N.M. Moutsopoulos, Human oral mucosa cell atlas reveals a stromal-neutrophil axis regulating tissue immunity, Cell 184 (15) (2021), https://doi.org/10.1016/j.cell.2021.05.013, 4090–4104.e15.

[27] A. Borenstein, N. Fine, S. Hassanpour, C. Sun, M. Oveisi, H.C. Tenenbaum, M. Glogauer, Morphological characterization of para- and proinflammatory neutrophil phenotypes using transmission electron microscopy, J. Periodontal. Res. 53 (6) (2018) 972–982, https://doi.org/10.1111/jre.12595.

[28] M.A. del Pozo, R. Pulido, C. Muñoz, V. Alvarez, A. Humbría, M.R. Campanero, F. Sánchez-Madrid, Regulation of ICAM-3 (CD50) membrane expression on human neutrophils through a proteolytic shedding mechanism, Eur. J. Immunol. 24 (11) (1994) 2586–2594, https://doi.org/10.1002/eji.1830241104.

[29] K.L. Davenpeck, M.E. Brummet, S.A. Hudson, R.J. Mayer, B.S. Bochner, Activation of human leukocytes reduces surface P-selectin glycoprotein ligand-1 (PSGL-1, CD162) and adhesion to P-selectin in vitro, J. Immunol. 165 (5) (2000) 2764–2772, https://doi.org/10.4049/jimmunol.165.5.2764 (Baltimore, Md. : 1950).

[30] F.S. Lakschevitz, S. Hassanpour, A. Rubin, N. Fine, C. Sun, M. Glogauer, Identification of neutrophil surface marker changes in health and inflammation using high-throughput screening flow cytometry, Exp. Cell Res. 342 (2) (2016) 200–209, https://doi.org/10.1016/j.yexcr.2016.03.007.

[31] N.T. Luu, G.E. Rainger, C.D. Buckley, G.B. Nash, CD31 regulates direction and rate of neutrophil migration over and under endothelial cells, J. Vasc. Res. 40 (5) (2003) 467–479, https://doi.org/10.1159/000074296.

[32] Y. Katayama, A. Hidalgo, J. Chang, A. Peired, P.S. Frenette, CD44 is a physiological E-selectin ligand on neutrophils, J. Exp. Med. 201 (8) (2005) 1183–1189, https://doi.org/10.1084/jem.20042014.

[33] G. Zuchtriegel, B. Uhl, M.E. Hessenauer, A.R. Kurz, M. Rehberg, K. Lauber, F. Krombach, C.A. Reichel, Spatiotemporal expression dynamics of selectins govern the sequential extravasation of neutrophils and monocytes in the acute inflammatory response, Arterioscler. Thromb. Vasc. Biol. 35 (4) (2015) 899–910, https://doi.org/10.1161/ATVBAHA.114.305143.

[34] N. Kato, Y. Yuzawa, T. Kosugi, A. Hobo, W. Sato, Y. Miwa, K. Sakamoto, S. Matsuo, K. Kadomatsu, The E-selectin ligand basigin/CD147 is responsible for neutrophil recruitment in renal ischemia/reperfusion, J. Am. Soc. Nephrol. 20 (7) (2009) 1565–1576, https://doi.org/10.1681/ASN.2008090957.

[35] A. Capucetti, F. Albano, R. Bonecchi, Multiple roles for chemokines in neutrophil biology, Front. Immunol. 11 (2020) 1259, https://doi.org/10.3389/fimmu.2020.01259.

[36] A. Woodfin, C.A. Reichel, A. Khandoga, M. Corada, M.B. Voisin, C. Scheiermann, D.O. Haskard, E. Dejana, F. Krombach, S. Nourshargh, JAM-A mediates neutrophil transmigration in a stimulus-specific manner in vivo: evidence for sequential roles for JAM-A and PECAM-1 in neutrophil transmigration, Blood 110 (6) (2007) 1848–1856, https://doi.org/10.1182/blood-2006-09-047431.

[37] S. Baruah, S. Murthy, K. Keck, I. Galvan, A. Prichard, L.H. Allen, M. Farrelly, J. Klesney-Tait, TREM-1 regulates neutrophil chemotaxis by promoting NOX-dependent superoxide production, J. Leukoc. Biol. 105 (6) (2019) 1195–1207, https://doi.org/10.1002/JLB.3VMA0918-375R.

[38] Y. Wang, J. Wu, R. Newton, N.S. Bahaie, C. Long, B. Walcheck, ADAM17 cleaves CD16b (FcγRIIIb) in human neutrophils, Biochim. Biophys. Acta 1833 (3) (2013) 680–685, https://doi.org/10.1016/j.bbamcr.2012.11.027.

[39] P. Rieu, F. Porteu, G. Bessou, P. Lesavre, L. Halbwachs-Mecarelli, Human neutrophils release their major membrane sialoprotein, leukosialin (CD43), during cell activation, Eur. J. Immunol. 22 (11) (1992) 3021–3026, https://doi.org/10.1002/eji.1830221138.

[40] M. Yamamoto, K. Saeki, K. Utsumi, Isolation of human salivary polymorphonuclear leukocytes and their stimulation-coupled responses, Arch. Biochem. Biophys. 289 (1) (1991) 76–82, https://doi.org/10.1016/0003-9861(91)90444-n.

[41] C.G.J. Moonen, J. Hirschfeld, L. Cheng, I.L.C. Chapple, B.G. Loos, E.A. Nicu, Oral neutrophils characterized: chemotactic, phagocytic, and neutrophil extracellular trap (NET) formation properties, Front. Immunol. 10 (2019) 635, https://doi.org/10.3389/fimmu.2019.00635.

[42] K.M. Skubitz, K.D. Campbell, J. Iida, A.P. Skubitz, CD63 associates with tyrosine kinase activity and CD11/CD18, and transmits an activation signal in neutrophils, J. Immunol. 157 (8) (1996) 3617–3626.

[43] K.M. Skubitz, K.D. Campbell, A.P. Skubitz, CD66a, CD66b, CD66c, and CD66d each independently stimulate neutrophils, J. Leukoc. Biol. 60 (1) (1996) 106–117, https://doi.org/10.1002/jlb.60.1.106.

[44] H. Tapper, S. Grinstein, Fc receptor-triggered insertion of secretory granules into the plasma membrane of human neutrophils: selective retrieval during phagocytosis, J. Immunol. 159 (1) (1997) 409–418.

[45] J. Donadieu, S. Frenz, L. Merz, F. Sicre De Fontbrune, G.A. Rotulo, B. Beaupain, M. Biosse-Duplan, M. Audrain, L. Croisille, P. Ancliff, C. Klein, C. Bellanné-Chantelot, Chronic neutropenia: how best to assess severity and approach management? Expet Rev. Hematol. 14 (10) (2021) 945–960, https://doi.org/10.1080/17474086.2021.1976634.

[46] C. Gibson, N. Berliner, How we evaluate and treat neutropenia in adults, Blood 124 (8) (2014) 1251–1378, https://doi.org/10.1182/blood-2014-02-482612.

[47] J. Bux, K. Kissel, K. Nowak, U. Spengel, C. Mueller-Eckhardt, Autoimmune neutropenia: clinical and laboratory studies in 143 patients, Ann. Hematol. 63 (5) (1991) 249–252, https://doi.org/10.1007/BF01698373.

[48] M. Pac, D. Olczak-Kowalczyk, B. Wolska-KuÅ)nierz, B. PiÄ…tosa, R. Gá^{3}rska, E. Bernatowska, Recurrent oral inflammation in autoimmune lymphoproliferative syndrome, J. Pediatr. Neurosci. 6 (2014) e211, https://doi.org/10.17334/JPS.49665.

[49] C.C. Dixon, F.J. Thomson, S.M. Barry, Oral manifestations of autoimmune neutropenia: a case report, J. Clin. Pediatr. Dent 43 (1) (2019) 46–50, https://doi.org/10.17796/1053-4625-43.1.9.

[50] L. Ibáñez, X. Vidal, E. Ballarín, J.R. Laporte, Population-based drug-induced agranulocytosis, Arch. Intern. Med. 165 (8) (2005) 869–874, https://doi.org/10.1001/archinte.165.8.869.

[51] M. Kishimoto, M. Akashi, K. Tsuji, J. Kusumoto, S. Furudoi, Y. Shibuya, Y. Inui, K. Yakushijin, S. Kawamoto, A. Okamura, H. Matsuoka, T. Komori, Intensity and duration of neutropenia relates to the development of oral mucositis but not odontogenic infection during chemotherapy for hematological malignancy, PLoS One 12 (7) (2017) e0182021, https://doi.org/10.1371/journal.pone.0182021.

[52] A. Lee, J. Hong, D.Y. Shin, Y. Koh, S.S. Yoon, P.J. Kim, H.G. Kim, I. Kim, H.K. Park, Y. Choi, Association of HSV-1 and reduced oral bacteriota diversity with chemotherapy-induced oral mucositis in patients undergoing autologous hematopoietic stem cell transplantation, J. Clin. Med. 9 (4) (2020) 1090, https://doi.org/10.3390/jcm9041090.

[53] J. Skokowa, D.C. Dale, I.P. Touw, C. Zeidler, K. Welte, Severe congenital neutropenias, Nat. Rev. Dis. Prim. 3 (2017) 17032, https://doi.org/10.1038/nrdp.2017.32.

[54] J. Donadieu, B. Beaupain, O. Fenneteau, C. Bellanné-Chantelot, Congenital neutropenia in the era of genomics: classification, diagnosis, and natural history, Br. J. Haematol. 179 (4) (2017) 557–574, https://doi.org/10.1111/bjh.14887.

[55] D.C. Dale, R.E. Person, A.A. Bolyard, A.G. Aprikyan, C. Bos, M.A. Bonilla, L.A. Boxer, G. Kannourakis, C. Zeidler, K. Welte, K.F. Benson, M. Horwitz, Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia, Blood 96 (7) (2000) 2317–2322.

[56] G.A. Rotulo, G. Plat, B. Beaupain, S. Blanche, D. Moushous, F. Sicre de Fontbrune, T. Leblanc, C. Renard, V. Barlogis, M.G. Vigue, C. Freycon, C. Piguet, M. Pasquet, C. Fieschi, W. Abou-Chahla, V. Gandemer, F. Rialland, F. Millot, A. Marie-Cardine, C. Paillard, French Severe Chronic Neutropenia Registry, Recurrent bacterial infections, but not fungal infections, characterise patients with ELANE-related neutropenia: a French Severe Chronic Neutropenia Registry study, Br. J. Haematol. 194 (5) (2021) 908–920, https://doi.org/10.1111/bjh.17695.

[57] C. Klein, M. Grudzien, G. Appaswamy, M. Germeshausen, I. Sandrock, A.A. Schäffer, C. Rathinam, K. Boztug, B. Schwinzer, N. Rezaei, G. Bohn, M. Melin, G. Carlsson, B. Fadeel, N. Dahl, J. Palmblad, J.I. Henter, C. Zeidler, B. Grimbacher, K. Welte, HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease), Nat. Genet. 39 (1) (2007) 86–92, https://doi.org/10.1038/ng1940.

[58] R. Kostman, Infantile genetic agranulocytosis. A review with presentation of ten new cases, Acta Paediatr. Scand. 64 (2) (1975) 362–368, https://doi.org/10.1111/j.1651-2227.1975.tb03847.x.

[59] K. Boztug, P.M. Järvinen, E. Salzer, T. Racek, S. Mönch, W. Garncarz, E.M. Gertz, A.A. Schäffer, A. Antonopoulos, S.M. Haslam, L. Schieck, J. Puchałka, J. Diestelhorst, G. Appaswamy, B. Lescoeur, R. Giambruno, J.W. Bigenzahn, U. Elling, D. Pfeifer, C.D. Conde, C. Klein, JAGN1 deficiency causes aberrant myeloid cell homeostasis and congenital neutropenia, Nat. Genet. 46 (9) (2014) 1021–1027, https://doi.org/10.1038/ng.3069.

[60] A. Triot, P.M. Järvinen, J.I. Arostegui, D. Murugan, N. Kohistani, J.L. Dapena Díaz, T. Racek, J. Puchałka, E.M. Gertz, A.A. Schäffer, D. Kotlarz, D. Pfeifer, C. Díaz de Heredia Rubio, M.A. Ozdemir, T. Patiroglu, M. Karakukcu, J. Sánchez de Toledo Codina, J. Yagüe, I.P. Touw, E. Unal, C. Klein, Inherited biallelic CSF3R mutations in severe congenital neutropenia, Blood 123 (24) (2014) 3811–3817, https://doi.org/10.1182/blood-2013-11-535419.
[61] E. Van Nieuwenhove, J.S. Barber, J. Neumann, E. Smeets, M. Willemsen, E. Pasciuto, T. Prezzemolo, V. Lagou, L. Seldeslachts, B. Malengier-Devlies, M. Metzemaekers, S. Haßdenteufel, A. Kerstens, R. van der Kant, F. Rousseau, J. Schymkowitz, D. Di Marino, S. Lang, R. Zimmermann, S. Schlenner, A. Liston, Defective Sec61α1 underlies a novel cause of autosomal dominant severe congenital neutropenia, J. Allergy Clin. Immunol. 146 (5) (2020) 1180–1193, https://doi.org/10.1016/j.jaci.2020.03.034.
[62] C. Bellanné-Chantelot, B. Schmaltz-Panneau, C. Marty, O. Fenneteau, I. Callebaut, S. Clauin, A. Docet, G.L. Damaj, T. Leblanc, I. Pellier, C. Stoven, S. Souquere, I. Antony-Debré, B. Beaupain, N. Aladjidi, V. Barlogis, F. Bauduer, P. Bensaid, O. Boespflug-Tanguy, C. Berger, J. Donadieu, Mutations in the *SRP54* gene cause severe congenital neutropenia as well as Shwachman-Diamond-like syndrome, Blood 132 (12) (2018) 1318–1331, https://doi.org/10.1182/blood-2017-12-820308.
[63] B. Schmaltz-Panneau, A. Pagnier, S. Clauin, J. Buratti, C. Marty, O. Fenneteau, K. Dieterich, B. Beaupain, J. Donadieu, I. Plo, C. Bellanné-Chantelot, Identification of biallelic germline variants of SRP68 in a sporadic case with severe congenital neutropenia, Haematologica 106 (4) (2021) 1216–1219, https://doi.org/10.3324/haematol.2020.247825.
[64] V. Makaryan, E.A. Rosenthal, A.A. Bolyard, M.L. Kelley, J.E. Below, M.J. Bamshad, K.M. Bofferding, J.D. Smith, K. Buckingham, L.A. Boxer, J. Skokowa, K. Welte, D.A. Nickerson, G.P. Jarvik, D.C. Dale, UW Center for Mendelian Genomics, TCIRG1-associated congenital neutropenia, Hum. Mutat. 35 (7) (2014) 824–827, https://doi.org/10.1002/humu.22563.
[65] K. Devriendt, A.S. Kim, G. Mathijs, S.G. Frints, M. Schwartz, J.J. Van Den Oord, G.E. Verhoef, M.A. Boogaerts, J.P. Fryns, D. You, M.K. Rosen, P. Vandenberghe, Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia, Nat. Genet. 27 (3) (2001) 313–317, https://doi.org/10.1038/85886.
[66] M. Keszei, J. Record, J.S. Kritikou, H. Wurzer, C. Geyer, M. Thiemann, P. Drescher, H. Brauner, L. Köcher, J. James, M. He, M.A. Baptista, C.I. Dahlberg, A. Biswas, D.P. Lane, W. Song, K. Pütsep, P. Vandenberghe, S.B. Snapper, L.S. Westerberg, Constitutive activation of WASp in X-linked neutropenia renders neutrophils hyperactive, J. Clin. Investig. 128 (9) (2018) 4115–4131, https://doi.org/10.1172/JCI64772.
[67] M. Horwitz, K.F. Benson, R.E. Person, A.G. Aprikyan, D.C. Dale, Mutations in ELA2, encoding neutrophil elastase, define a 21-day biological clock in cyclic haematopoiesis, Nat. Genet. 23 (4) (1999) 433–436, https://doi.org/10.1038/70544.
[68] P.G. Barth, R.J. Wanders, P. Vreken, E.A. Janssen, J. Lam, F. Baas, X-linked cardioskeletal myopathy and neutropenia (Barth syndrome) (MIM 302060), J. Inherit. Metab. Dis. 22 (4) (1999) 555–567, https://doi.org/10.1023/a:1005568609936.
[69] S.L. Clarke, A. Bowron, I.L. Gonzalez, S.J. Groves, R. Newbury-Ecob, N. Clayton, R.P. Martin, B. Tsai-Goodman, V. Garratt, M. Ashworth, V.M. Bowen, K. R. McCurdy, M.K. Damin, C.T. Spencer, M.J. Toth, R.I. Kelley, C.G. Steward, Barth syndrome, Orphanet J. Rare Dis. 8 (2013) 23, https://doi.org/10.1186/1750-1172-8-23.
[70] H.S. Jun, D.A. Weinstein, Y.M. Lee, B.C. Mansfield, J.Y. Chou, Molecular mechanisms of neutrophil dysfunction in glycogen storage disease type Ib, Blood 123 (18) (2014) 2843–2853, https://doi.org/10.1182/blood-2013-05-502435.
[71] D.C. Dale, A.A. Bolyard, T. Marrero, M.L. Kelley, V. Makaryan, E. Tran, J. Leung, L.A. Boxer, P.S. Kishnani, S. Austin, C. Wanner, I.A. Ferrecchia, D. Khalaf, D. Maze, J. Kurtzberg, C. Zeidler, K. Welte, D.A. Weinstein, Neutropenia in glycogen storage disease Ib: outcomes for patients treated with granulocyte colony-stimulating factor, Curr. Opin. Hematol. 26 (1) (2019) 16–21, https://doi.org/10.1097/MOH.0000000000000474.
[72] J. Kolehmainen, G.C. Black, A. Saarinen, K. Chandler, J. Clayton-Smith, A.L. Träskelin, R. Perveen, S. Kivitie-Kallio, R. Norio, M. Warburg, J.P. Fryns, A. de la Chapelle, A.E. Lehesjoki, Cohen syndrome is caused by mutations in a novel gene, COH1, encoding a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport, Am. J. Hum. Genet. 72 (6) (2003) 1359–1369, https://doi.org/10.1086/375454.
[73] M.J. Falk, H.S. Feiler, D.E. Neilson, K. Maxwell, J.V. Lee, S.K. Segall, N.H. Robin, K.C. Wilhelmsen, A.L. Träskelin, J. Kolehmainen, A.E. Lehesjoki, M. Wiznitzer, M.L. Warman, Cohen syndrome in the Ohio amish, Am. J. Med. Genet. 128A (1) (2004) 23–28, https://doi.org/10.1002/ajmg.a.30033.
[74] N. Güneş, D.U. Alkaya, V. Demirbilek, C. Yalçınkaya, B. Tüysüz, Early diagnostic signs and the natural history of typical findings in cohen syndrome, J. Pediatr. 252 (2023) 93–100, https://doi.org/10.1016/j.jpeds.2022.08.052.
[75] L. Volpi, G. Roversi, E.A. Colombo, N. Leijsten, D. Concolino, A. Calabria, M.A. Mencarelli, M. Fimiani, F. Macciardi, R. Pfundt, E.F. Schoenmakers, L. Larizza, Targeted next-generation sequencing appoints c16orf57 as clericuzio-type poikiloderma with neutropenia gene, Am. J. Hum. Genet. 86 (1) (2010) 72–76, https://doi.org/10.1016/j.ajhg.2009.11.014.
[76] R. Chantorn, T. Shwayder, Poikiloderma with neutropenia: report of three cases including one with calcinosis cutis, Pediatr. Dermatol. 29 (4) (2012) 463–472, https://doi.org/10.1111/j.1525-1470.2011.01513.x.
[77] D. Concolino, S. Sestito, F. Falvo, G. Romano, M. Ceravolo, E. Anastasio, L. Pensabene, E.A. Colombo, L. Larizza, Assessment of intrafamilial clinical variability of poikiloderma with neutropenia by a 10-year follow-up of three affected siblings, Eur. J. Med. Genet. 62 (1) (2019) 73–76, https://doi.org/10.1016/j.ejmg.2018.05.007.
[78] H. Gangadharan, K. Singh, S. Phadke, A. Aggarwal, Clinical sequencing solves a diagnostic dilemma by identifying a novel pathogenic variant in USB1 gene causing poikiloderma with neutropenia, Indian J. Pediatr. 88 (3) (2021) 270–271, https://doi.org/10.1007/s12098-020-03502-w.
[79] V. Piccolo, T. Russo, D. Di Pinto, E. Pota, M. Di Martino, G. Piluso, A. Ronchi, G. Argenziano, E.V. Di Brizzi, C. Santoro, Poikiloderma with neutropenia and mastocytosis: a case report and a review of dermatological signs, Front. Med. 8 (2021) 680363, https://doi.org/10.3389/fmed.2021.680363.
[80] M. Delépine, M. Nicolino, T. Barrett, M. Golamaully, G.M. Lathrop, C. Julier, EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome, Nat. Genet. 25 (4) (2000) 406–409, https://doi.org/10.1038/78085.
[81] C.A. Crowley, J.T. Curnutte, R.E. Rosin, J. André-Schwartz, J.I. Gallin, M. Klempner, R. Snyderman, F.S. Southwick, T.P. Stossel, B.M. Babior, An inherited abnormality of neutrophil adhesion. Its genetic transmission and its association with a missing protein, N. Engl. J. Med. 302 (21) (1980) 1163–1168, https://doi.org/10.1056/NEJM198005223022102.
[82] A.E. Novoa, S. Kasbekar, A.J. Thrasher, D.B. Kohn, J. Sevilla, T. Nguyen, J.D. Schwartz, J.A. Bueren, Leukocyte adhesion deficiency-I: a comprehensive review of all published cases, J. Allergy Clin. Immunol. 6 (4) (2018) 1418–1420.e10, https://doi.org/10.1016/j.jaip.2017.12.008. *In practice*.
[83] A. Etzioni, M. Frydman, S. Pollack, I. Avidor, M.L. Phillips, J.C. Paulson, R. Gershoni-Baruch, Brief report: recurrent severe infections caused by a novel leukocyte adhesion deficiency, N. Engl. J. Med. 327 (25) (1992) 1789–1792, https://doi.org/10.1056/NEJM199212173272505.
[84] A. Etzioni, M. Tonetti, Leukocyte adhesion deficiency II-from A to almost Z, Immunol. Rev. 178 (2000) 138–147, https://doi.org/10.1034/j.1600-065x.2000.17805.x.
[85] R. Alon, A. Etzioni, LAD-III, a novel group of leukocyte integrin activation deficiencies, Trends Immunol. 24 (10) (2003) 561–566, https://doi.org/10.1016/j.it.2003.08.001.
[86] T.W. Kuijpers, E. van de Vijver, M.A. Weterman, M. de Boer, A.T. Tool, T.K. van den Berg, M. Moser, M.E. Jakobs, K. Seeger, O. Sanal, S. Unal, M. Cetin, D. Roos, A.J. Verhoeven, F. Baas, LAD-1/variant syndrome is caused by mutations in FERMT3, Blood 113 (19) (2009) 4740–4746, https://doi.org/10.1182/blood-2008-10-182154.
[87] D.B. Kuhns, D.L. Fink, U. Choi, C. Sweeney, K. Lau, D.L. Priel, D. Riva, L. Mendez, G. Uzel, A.F. Freeman, K.N. Olivier, V.L. Anderson, R. Currens, V. Mackley, A. Kang, M. Al-Adeli, E. Mace, J.S. Orange, E. Kang, S.J. Lockett, S.M. Holland, Cytoskeletal abnormalities and neutrophil dysfunction in WDR1 deficiency, Blood 128 (17) (2016) 2135–2143, https://doi.org/10.1182/blood-2016-03-706028.
[88] L. Pfajfer, N.K. Mair, R. Jiménez-Heredia, F. Genel, N. Gulez, Ö. Ardeniz, B. Hoeger, S.K. Bal, C. Madritsch, A. Kalinichenko, R. Chandra Ardy, B. Gerçeker, J. Rey-Barroso, H. Ijspeert, S.G. Tangye, I. Simonitsch-Klupp, J.B. Huppa, M. van der Burg, L. Dupré, K. Boztug, Mutations affecting the actin regulator WD repeat-containing protein 1 lead to aberrant lymphoid immunity, J. Allergy Clin. Immunol. 142 (5) (2018) 1589–1604.e11, https://doi.org/10.1016/j.jaci.2018.04.023.

[89] A.S. Standing, D. Malinova, Y. Hong, J. Record, D. Moulding, M.P. Blundell, K. Nowak, H. Jones, E. Omoyinmi, K.C. Gilmour, A. Medlar, H. Stanescu, R. Kleta, G. Anderson, S. Nanthapisal, S.M. Gomes, N. Klein, D. Eleftheriou, A.J. Thrasher, P.A. Brogan, Autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia (PFIT) caused by mutation in actin-regulatory gene WDR1, J. Exp. Med. 214 (1) (2017) 59–71, https://doi.org/10.1084/jem.20161228.
[90] C. Toomes, J. James, A.J. Wood, C.L. Wu, D. McCormick, N. Lench, C. Hewitt, L. Moynihan, E. Roberts, C.G. Woods, A. Markham, M. Wong, R. Widmer, K. A. Ghaffar, M. Pemberton, I.R. Hussein, S.A. Temtamy, R. Davies, A.P. Read, P. Sloan, N.S. Thakker, Loss-of-function mutations in the cathepsin C gene result in periodontal disease and palmoplantar keratosis, Nat. Genet. 23 (4) (1999) 421–424, https://doi.org/10.1038/70525.
[91] H. Roberts, P. White, I. Dias, S. McKaig, R. Veeramachaneni, N. Thakker, M. Grant, I. Chapple, Characterization of neutrophil function in Papillon-Lefèvre syndrome, J. Leukoc. Biol. 100 (2) (2016) 433–444, https://doi.org/10.1189/jlb.5A1015-489R.
[92] P. Sharma, E.R. Nicoli, J. Serra-Vinardell, M. Morimoto, C. Toro, M.C.V. Malicdan, W.J. Introne, Chediak-Higashi syndrome: a review of the past, present, and future, Drug Discov. Today Dis. Model. 31 (2020) 31–36, https://doi.org/10.1016/j.ddmod.2019.10.008.
[93] W. Introne, R.E. Boissy, W.A. Gahl, Clinical, molecular, and cell biological aspects of Chediak-Higashi syndrome, Mol. Genet. Metabol. 68 (2) (1999) 283–303, https://doi.org/10.1006/mgme.1999.2927.
[94] J.A.A. de Arruda, S.S. Sousa-Neto, L.G. Abreu, L.F. Schuch, V.G. Souza, T.V.L. Alves, B. Martins-Andrade, S.S. Shetty, J.L.G.C. Monteiro, E.F. Mendonça, R. A. Mesquita, G. Callou, Oral manifestations of Chediak-Higashi syndrome: a systematic review, Disease-a-Month : DM 69 (1) (2023) 101356, https://doi.org/10.1016/j.disamonth.2022.101356.
[95] J.A. Lekstrom-Himes, S.E. Dorman, P. Kopar, S.M. Holland, J.I. Gallin, Neutrophil-specific granule deficiency results from a novel mutation with loss of function of the transcription factor CCAAT/enhancer binding protein epsilon, J. Exp. Med. 189 (11) (1999) 1847–1852, https://doi.org/10.1084/jem.189.11.1847.
[96] L.A. Boxer, T.D. Coates, R.A. Haak, J.B. Wolach, S. Hoffstein, R.L. Baehner, Lactoferrin deficiency associated with altered granulocyte function, N. Engl. J. Med. 307 (7) (1982) 404–410, https://doi.org/10.1056/NEJM198208123070704.
[97] D.R. Ambruso, M. Sasada, H. Nishiyama, A. Kubo, A. Komiyama, R.H. Allen, Defective bactericidal activity and absence of specific granules in neutrophils from a patient with recurrent bacterial infections, J. Clin. Immunol. 4 (1) (1984) 23–30, https://doi.org/10.1007/BF00915283.
[98] J.I. Gallin, M.P. Fletcher, B.E. Seligmann, S. Hoffstein, K. Cehrs, N. Mounessa, Human neutrophil-specific granule deficiency: a model to assess the role of neutrophil-specific granules in the evolution of the inflammatory response, Blood 59 (6) (1982) 1317–1329.
[99] E. Song, G.B. Jaishankar, H. Saleh, W. Jithpratuck, R. Sahni, G. Krishnaswamy, Chronic granulomatous disease: a review of the infectious and inflammatory complications, Clin. Mol. Allergy 9 (1) (2011) 10, https://doi.org/10.1186/1476-7961-9-10.
[100] J.M. van den Berg, E. van Koppen, A. Ahlin, B.H. Belohradsky, E. Bernatowska, L. Corbeel, T. Español, A. Fischer, M. Kurenko-Deptuch, R. Mouy, T. Petropoulou, J. Roesler, R. Seger, M.J. Stasia, N.H. Valerius, R.S. Weening, B. Wolach, D. Roos, T.W. Kuijpers, Chronic granulomatous disease: the European experience, PLoS One 4 (4) (2009) e5234, https://doi.org/10.1371/journal.pone.0005234.
[101] J. Liese, S. Kloos, V. Jendrossek, T. Petropoulou, U. Wintergerst, G. Notheis, M. Gahr, B.H. Belohradsky, Long-term follow-up and outcome of 39 patients with chronic granulomatous disease, J. Pediatr. 137 (5) (2000) 687–693, https://doi.org/10.1067/mpd.2000.109112.
[102] H.T. Akar, S. Esenboga, D. Cagdas, S.O. Halacli, B. Ozbek, K. van Leeuwen, M. de Boer, C.S. Tan, Y. Köker, D. Roos, I. Tezcan, Clinical and immunological characteristics of 63 patients with chronic granulomatous disease: hacettepe experience, J. Clin. Immunol. 41 (5) (2021) 992–1003, https://doi.org/10.1007/s10875-021-01002-w.
[103] Q. Zhou, X. Hui, W. Ying, J. Hou, W. Wang, D. Liu, Y. Wang, Y. Yu, J. Wang, J. Sun, Q. Zhang, X. Wang, A cohort of 169 chronic granulomatous disease patients exposed to BCG vaccination: a retrospective study from a single center in Shanghai, China (2004-2017), J. Clin. Immunol. 38 (3) (2018) 260–272, https://doi.org/10.1007/s10875-018-0486-y.
[104] B. Martire, R. Rondelli, A. Soresina, C. Pignata, T. Broccoletti, A. Finocchi, P. Rossi, M. Gattorno, M. Rabusin, C. Azzari, R.M. Dellepiane, M.C. Pietrogrande, A. Trizzino, P. Di Bartolomeo, S. Martino, L. Carpino, F. Cossu, F. Locatelli, R. Maccario, P. Pierani, Ipinet, Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study, Clinical immunology (Orlando, Fla 126 (2) (2008) 155–164, https://doi.org/10.1016/j.clim.2007.09.008.
[105] N. Bejjani, B. Beaupain, Y. Bertrand, C. Bellanne-Chantelot, J. Donadieu, How to differentiate congenital from noncongenital chronic neutropenia at the first medical examination? Proposal of score: a pilot study from the French Severe Chronic Neutropenia registry, Pediatr. Blood Cancer 64 (2017) e26722, https://doi.org/10.1002/pbc.26722.
[106] P.J. Ancliff, M.P. Blundell, G.O. Cory, Y. Calle, A. Worth, H. Kempski, S. Burns, G.E. Jones, J. Sinclair, C. Kinnon, I.M. Hann, R.E. Gale, D.C. Linch, A. J. Thrasher, Two novel activating mutations in the Wiskott-Aldrich syndrome protein result in congenital neutropenia, Blood 108 (7) (2006) 2182–2189, https://doi.org/10.1182/blood-2006-01-010249.
[107] K. Beel, M.M. Cotter, J. Blatny, J. Bond, G. Lucas, F. Green, V. Vanduppen, D.W. Leung, S. Rooney, O.P. Smith, M.K. Rosen, P. Vandenberghe, A large kindred with X-linked neutropenia with an I294T mutation of the Wiskott-Aldrich syndrome gene, Br. J. Haematol. 144 (1) (2009) 120–126, https://doi.org/10.1111/j.1365-2141.2008.07416.x.
[108] B. Wolach, R. Gavrieli, O. Wolach, T. Stauber, O. Abuzaitoun, A. Kuperman, Y. Amir, P. Stepensky, R. Somech, A. Etzioni, Leucocyte adhesion deficiency-A multicentre national experience, Eur. J. Clin. Invest. 49 (2) (2019) e13047, https://doi.org/10.1111/eci.13047.
[109] N.M. Moutsopoulos, J. Konkel, M. Sarmadi, M.A. Eskan, T. Wild, N. Dutzan, L. Abusleme, C. Zenobia, K.B. Hosur, T. Abe, G. Uzel, W. Chen, T. Chavakis, S. M. Holland, G. Hajishengallis, Defective neutrophil recruitment in leukocyte adhesion deficiency type I disease causes local IL-17-driven inflammatory bone loss, Sci. Transl. Med. 6 (229) (2014) 229ra40, https://doi.org/10.1126/scitranslmed.3007696.
[110] N.M. Moutsopoulos, C.S. Zerbe, T. Wild, N. Dutzan, L. Brenchley, G. DiPasquale, G. Uzel, K.C. Axelrod, A. Lisco, L.D. Notarangelo, G. Hajishengallis, L. D. Notarangelo, S.M. Holland, Interleukin-12 and interleukin-23 blockade in leukocyte adhesion deficiency type 1, N. Engl. J. Med. 376 (12) (2017) 1141–1146, https://doi.org/10.1056/NEJMoa1612197.
[111] B. Fournier, B. Neven, S. Chhun, S. Blanche, M. Biosse Duplan, Oral ulcers resolution using IL12/23 blockade in an infant with leukocyte adhesion deficiency type 1, J. Clin. Immunol. 42 (4) (2022) 907–909, https://doi.org/10.1007/s10875-022-01253-1.
[112] S. Tur-Gracia, N. Martinez-Quiles, Emerging functions of cytoskeletal proteins in immune diseases, J. Cell Sci. 134 (3) (2021) jcs253534, https://doi.org/10.1242/jcs.253534.
[113] S.F. de Haar, D.C. Jansen, T. Schoenmaker, H. De Vree, V. Everts, W. Beertsen, Loss-of-function mutations in cathepsin C in two families with Papillon-Lefèvre syndrome are associated with deficiency of serine proteinases in PMNs, Hum. Mutat. 23 (5) (2004) 524, https://doi.org/10.1002/humu.9243.
[114] O.E. Sørensen, S.N. Clemmensen, S.L. Dahl, O. Østergaard, N.H. Heegaard, A. Glenthøj, F.C. Nielsen, N. Borregaard, Papillon-Lefèvre syndrome patient reveals species-dependent requirements for neutrophil defenses, J. Clin. Investig. 124 (10) (2014) 4539–4548, https://doi.org/10.1172/JCI76009.
[115] C.T. Pham, J.L. Ivanovich, S.Z. Raptis, B. Zehnbauer, T.J. Ley, Papillon-Lefèvre syndrome: correlating the molecular, cellular, and clinical consequences of cathepsin C/dipeptidyl peptidase I deficiency in humans, J. Immunol. 173 (12) (2004) 7277–7281, https://doi.org/10.4049/jimmunol.173.12.7277.
[116] L. Giannetti, R. Apponi, A.M. Dello Diago, M. Jafferany, M. Goldust, R. Sadoughifar, Papillon-Lefèvre syndrome: oral aspects and treatment, Dermatol. Ther. 33 (3) (2020) e13336, https://doi.org/10.1111/dth.13336.
[117] G. Nussbaum, L. Shapira, How has neutrophil research improved our understanding of periodontal pathogenesis? J. Clin. Periodontol. 38 (Suppl 11) (2011) 49–59, https://doi.org/10.1111/j.1600-051X.2010.01678.x.
[118] P.E. Newburger, H.J. Cohen, S.B. Rothchild, J.C. Hobbins, S.E. Malawista, M.J. Mahoney, Prenatal diagnosis of chronic granulomatous disease, N. Engl. J. Med. 300 (4) (1979) 178–181, https://doi.org/10.1056/NEJM197901253000406.
[119] J. Schaller, Illness resembling lupus erythematosus in mothers of boys with chronic granulomatous disease, Ann. Intern. Med. 76 (5) (1972) 747–750, https://doi.org/10.7326/0003-4819-76-5-747.
[120] K. Kragballe, N. Borregaard, F. Brandrup, C. Koch, K. Staehrjohansen, Relation of monocyte and neutrophil oxidative metabolism to skin and oral lesions in carriers of chronic granulomatous disease, Clin. Exp. Immunol. 43 (2) (1981) 390–398.
[121] H.R. Stanley, Aphthous lesions, Oral Surg. Oral Med. Oral Pathol. 33 (3) (1972) 407–416, https://doi.org/10.1016/0030-4220(72)90470-7.

[122] T. Honma, T. Saito, Y. Fujioka, Possible role of apoptotic cells of the oral epithelium in the pathogenesis of aphthous ulceration, Oral Surg. Oral Med. Oral Pathol. 59 (1985) 379–387, https://doi.org/10.1016/0030-4220(85)90063-5.
[123] T. Lehner, Pathology of recurrent oral ulceration and oral ulceration in Behcet's syndrome: light, electron and fluorescence microscopy, J. Pathol. 97 (3) (1969) 481–494, https://doi.org/10.1002/path.1710970307.
[124] M.P. Mills, B.F. Mackler, D.C. Nelms, D.L. Peavy, Quantitative distribution of inflammatory cells in recurrent aphthous stomatitis, J. Dent. Res. 59 (3) (1980) 562–566, https://doi.org/10.1177/00220345800590030101.
[125] H.E. Schroeder, W. Müller-Glauser, K. Sallay, Pathomorphologic features of the ulcerative stage of oral aphthous ulcerations, Oral Surg. Oral Med. Oral Pathol. 58 (3) (1984) 293–305, https://doi.org/10.1016/0030-4220(84)90058-6.
[126] R. Häyrinen-Immonen, D. Nordström, M. Malmström, J. Hietanen, Y.T. Konttinen, Immune-inflammatory cells in recurrent oral ulcers (ROU), Scand. J. Dent. Res. 99 (6) (1991) 510–518, https://doi.org/10.1111/j.1600-0722.1991.tb01062.x.
[127] N.W. Savage, G.J. Seymour, B.J. Kruger, T-lymphocyte subset changes in recurrent aphthous stomatitis, Oral Surg. Oral Med. Oral Pathol. 60 (1985) 175–181, https://doi.org/10.1016/0030-4220(85)90287-7.
[128] A. Pedersen, B. Klausen, H.P. Hougen, J.P. Stenvang, T-lymphocyte subsets in recurrent aphthous ulceration, J. Oral Pathol. Med. 18 (1) (1989) 59–60, https://doi.org/10.1111/j.1600-0714.1989.tb00735.x.
[129] E. Ueta, M. Umazume, T. Yamamoto, T. Osaki, Leukocyte dysfunction in oral mucous membrane diseases, J. Oral Pathol. Med. 22 (1993) 120–125, https://doi.org/10.1111/j.1600-0714.1993.tb01042.x.
[130] S. Terzi, E. Dursun, A. Özgür, E. Yiğit, Z. Özergin-Coşkun, Ö. Çelebi-Erdivanl, M. Demirci, Status of neutrophils, lymphocytes and platelets in patients with recurrent aphthous stomatitis: a retrospective study, Iranian journal of otorhinolaryngology 28 (89) (2016) 421–424.
[131] S. Uluyol, S. Kilicaslan, Diagnostic value of neutrophil-lymphocyte ratios and mean platelet volumes in the activation of recurrent aphthous stomatitis, Indian Journal of Otolaryngology and Head and Neck Surgery 71 (1) (2019) 120–123, https://doi.org/10.1007/s12070-017-1059-8.
[132] S. Kayabasi, O. Hizli, S. Cayir, A novel predictor parameter for active recurrent aphthous stomatitis: C-reactive protein to albumin ratio, Cureus 11 (10) (2019) e5965, https://doi.org/10.7759/cureus.5965.
133 I.C. Karaer, Mean Platelet Volume, Neutrophil-To-Lymphocyte Ratio, and Platelet-To-Lymphocyte Ratio as İnflammatory Markers in patients with Recurrent Aphthous Stomatitis, The Eurasian Journal of Medicine 52 (1) (2020) 38–40, https://doi.org/10.5152/eurasianjmed.2019.18486.
[134] Ç. Turan, N. Metin, Z. Utlu, D. Tezcan, Mean platelet volume as a predictor in the differentiation of Behçet's disease from recurrent aphthous stomatitis - a single centre, prospective, case-control study, Int. J. Clin. Pract. 75 (11) (2021) e14866, https://doi.org/10.1111/ijcp.14866.
[135] F. Atalay, A. Kars, K. Topal, Z. Yavuz, Systemic immune inflammation index in patients with recurrent aphthous stomatitis, Brazilian Journal of Otorhinolaryngology 88 (4) (2022) 621–624, https://doi.org/10.1016/j.bjorl.2022.02.007.
[136] J.S. Lee, N.Y. Kim, S.H. Na, Y.H. Youn, C.S. Shin, Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea, Medicine 97 (26) (2018) e11138, https://doi.org/10.1097/MD.0000000000011138.
[137] X. Hao, D. Li, D. Wu, N. Zhang, The relationship between hematological indices and autoimmune rheumatic diseases (ARDs), a meta-analysis, Sci. Rep. 7 (1) (2017) 10833, https://doi.org/10.1038/s41598-017-11398-4.
[138] H. Haybar, S.M.S. Pezeshki, N. Saki, Evaluation of complete blood count parameters in cardiovascular diseases: an early indicator of prognosis? Exp. Mol. Pathol. 110 (2019) 104267 https://doi.org/10.1016/j.yexmp.2019.104267.
[139] P. Dagalis, J. Bagg, D.M. Walker, Spontaneous migration and chemotactic activity of neutrophil polymorphonuclear leukocytes in recurrent aphthous ulceration, Oral Surg. Oral Med. Oral Pathol. 64 (3) (1987) 298–301, https://doi.org/10.1016/0030-4220(87)90008-9.
[140] S. Sistig, A. Cekic-Arambasin, S. Rabatic, V. Vucicevic-Boras, J. Kleinheinz, J. Piffko, Natural immunity in recurrent aphthous ulceration, J. Oral Pathol. Med. 30 (5) (2001) 275–280, https://doi.org/10.1034/j.1600-0714.2001.300504.x.
[141] J. Lukac, M. Mravak-Stipetić, M. Knezević, J. Vrcek, S. Sistig, M. Ledinsky, Z. Kusić, Phagocytic functions of salivary neutrophils in oral mucous membrane diseases, J. Oral Pathol. Med. 32 (2003) 271–274, https://doi.org/10.1034/j.1600-0714.2003.00127.x.
[142] S. Altinor, S. Oztürkcan, M.M. Hah, The effects of colchicine on neutrophil function in subjects with recurrent aphthous stomatitis, J. Eur. Acad. Dermatol. Venereol. 17 (4) (2003) 469–470, https://doi.org/10.1046/j.1468-3083.2003.00614_1.x.
[143] B.P. Kumar, V. Keluskar, A.S. Bagewadi, A. Shetti, Evaluating and comparing phagocytic functions of salivary and blood neutrophils in patients with recurrent aphthous ulcers and controls, Quintessence Int. 41 (5) (2010) 411–416.
[144] D. Wray, J. Charon, Polymorphonuclear neutrophil function in recurrent aphthous stomatitis, J. Oral Pathol. Med. 20 (8) (1991) 392–394, https://doi.org/10.1111/j.1600-0714.1991.tb00951.x.
[145] N. Lewkowicz, P. Lewkowicz, A. Kurnatowska, M. Banasik, E. Glowacka, M. Cedzyński, A. Swierzko, B. Lauk-Puchala, H. Tchórzewski, Innate immune system is implicated in recurrent aphthous ulcer pathogenesis, J. Oral Pathol. Med. 32 (2003) 475–481, https://doi.org/10.1034/j.1600-0714.2003.00181.x.
[146] D.G. Wright, D.C. Dale, A.S. Fauci, S.M. Wolff, Human cyclic neutropenia: clinical review and long-term follow-up of patients, Medicine 60 (1) (1981) 1–13, https://doi.org/10.1097/00005792-198101000-00001.
[147] A. Ortega-Gómez, M. Perretti, O. Soehnlein, Resolution of inflammation: an integrated view, EMBO Mol. Med. 5 (5) (2013) 661–674, https://doi.org/10.1002/emmm.201202382.
[148] A. Das, M. Sinha, S. Datta, M. Abas, S. Chaffee, C.K. Sen, S. Roy, Monocyte and macrophage plasticity in tissue repair and regeneration, Am. J. Pathol. 185 (10) (2015) 2596–2606, https://doi.org/10.1016/j.ajpath.2015.06.001.
[149] G. Schett, M.F. Neurath, Resolution of chronic inflammatory disease: universal and tissue-specific concepts, Nat. Commun. 9 (1) (2018) 3261, https://doi.org/10.1038/s41467-018-05800-6.
[150] S. Ji, J. Hyun, E. Park, B.L. Lee, K.K. Kim, Y. Choi, Susceptibility of various oral bacteria to antimicrobial peptides and to phagocytosis by neutrophils, J. Periodontal. Res. 42 (5) (2007) 410–419, https://doi.org/10.1111/j.1600-0765.2006.00962.x.
[151] S. Ji, J.E. Shin, Y.C. Kim, Y. Choi, Intracellular degradation of Fusobacterium nucleatum in human gingival epithelial cells, Mol. Cell. 30 (6) (2010) 519–526, https://doi.org/10.1007/s10059-010-0142-8.
[152] K.J. Baek, S. Ji, Y.C. Kim, Y. Choi, Association of the invasion ability of Porphyromonas gingivalis with the severity of periodontitis, Virulence 6 (3) (2015) 274–281, https://doi.org/10.1080/21505594.2014.1000764.
[153] Y. Le, P.M. Murphy, J.M. Wang, Formyl-peptide receptors revisited, Trends Immunol. 23 (11) (2002) 541–548, https://doi.org/10.1016/s1471-4906(02)02316-5.
[154] A. Le Joncour, P. Cacoub, Y. Boulaftali, D. Saadoun, Neutrophil, NETs and Behçet's disease: a review, Clinical immunology (Orlando, Fla 250 (2023) 109318, https://doi.org/10.1016/j.clim.2023.109318.