REVIEW

Foamy Macrophages in Oral Lesions: An Insight

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Abstract

Introduction: The term "foamy" refers to "vacuolated cytoplasmic appearance of a macrophage" when viewed by light microscopy, due to the presence of lamellar bodies, accumulation of neutral lipids or drug particles in the cytoplasm of macrophages. Various studies had revealed the role of foamy macrophages in the pathogenesis of many oral lesions like verruciform xanthoma, periapical cysts, mucocele and pyogenic granuloma. This review focuses on the formation, pathogenesis and the role of foamy macrophages in various oral lesions.

Materials and Methods: A literature search was performed using MeSH terms in PubMed/Medline and Google Scholar databases and finally 18 articles were included.

Results: A total of 18 articles were included in this review. It includes case reports, review and original articles related to the topic foamy macrophages in oral lesions.

Conclusion: Foam cells contribute a pathognomonic diagnostic feature in certain oral lesions such as verruciform xanthoma. "Foamy macrophages" play a crucial role in both pathogenesis and diagnosis of oral lesions. Hence, a basic understanding of its formation and role in pathogenesis and diagnosis of certain oral lesions is essential.

Key words: Foamy macrophages, Histiocytes, Oral lesions

Introduction

Histiocytes are a type of immune cell and get differentiated from circulating monocytes. They help the body heal after an injury or infection by removing dead cells, micro-organisms, and foreign material from the body. Histiocytes that are laden with lipid (predominantly cholesterol), are called foamy histiocytes. The formation of foamy histiocytes have been reported in many pathologies associated with chronic infection[1] such as atherosclerosis, [2] septic arthritis etc. Various studies had revealed the role of foamy macrophages in the pathogenesis of many oral lesions like verruciform xanthoma, periapical cysts, mucocele and pyogenic granuloma.[3] Pathologists commonly encounter large groups of foamy histiocytes in tissue samples following an injury or infection. These cells can be visualised when the tissue is examined under the microscope using a routine stain called Hematoxylin and Eosin. However, a pathologist can perform a special test called immunohistochemistry to confirm the cells they are seeing under the microscope are histiocytes. When this test is performed, these cells will be positive or reactive for CD68 and CD163. This review highlights the pathogenesis of foamy macrophages and its role in various oral lesions.

Formation of foamy Macrophages

The induction of foam cell formation has several causes.

1. Phagocytosis of low-density lipoprotein (LDL).
2. The stimulation of macrophages by certain ligands,
3. Pathogen-induced signaling

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Phagocytosis of Low-Density Lipoproteins

The transition from macrophages to foam cells is a key step that occurs when fatty streaks are formed during the development of atherosclerotic plaques. The formation of foam cells occurs when macrophages engulf an excess of many types of LDL, including oxidized LDL (Ox LDL) and minimally modified LDL (mm LDL), which result in the death of the macrophages once they become oversaturated with LDLs. This occurs at fatty streaks, which is the early stage of atherosclerotic plaque development. The accumulation of foam cells contributes to the development of atherosclero-

sis by progressing plaque formation and causing the formation of unstable plaques.[17]

Lipid Signaling

Lipid polysaccharide (LPS) signals through toll-like receptor 4 (TLR4) to activate the immune response via the activation of NF-kB, AP-1 or IFN production. Ox LDL signals through TLR4, as well as CD36 and TLR6, which impairs the LPS-induce immune response and induces the formation of foam cells. This signaling changes the metabolic state of macrophages resulting in decreased cholesterol efflux, which causes increased foam cell formation.

Pathogen-Induced Signaling

Pathogens can induce the uptake of LDL by macrophages leading to the formation of foam cells. Porphyromonas gingivalis and Chlamydia pneumoniae are two pathogens that are believed to be associated with the development of atherosclerosis. Research using bone marrow-derived macrophages (BMDM) discovered that both P. gingivalis and C.Pneumoniae induce the formation of foam cells. Infection with both of these pathogens causes the secretion of cytokines, such as TNF-α and IL-6, while C.pneumoniae infection also causes IL-1β secretion. These changes lead to a proinflammatory response in macrophages, which contribute to the formation of foam cells.[17]

Classification

Inherited Metabolic Diseases

Lysosomal storage diseases

Infections

Mycobacteium tuberculosis
Chlamydia

Cystic Lesions

Mucocele
Periapical cyst

Tumors

Xanthogranuloma
Verruciform xanthoma
Central xanthoma

Lysosomal Storage Diseases

Lysosomes are membrane enclosed cytoplasmic organelles that contain a variety of different active hydrolytic enzymes (hydrolases). Mutations in genes encoding hydrolytic enzymes (hydrolase) will lead to the accumulation of the material meant for lysosomal degradation. There are about 50 groups of diseases found which are mostly autosomal inherited and few are X-linked inheritance. They are classified based on nature of primary stored material and protein defects.[6]

Lipid storage disorders:

a) Sphingolipidosis: Gaucher's disease, Niemann-Pick disease
b) Gangliosidosis: Tay-Sachs disease
c) Glycogen - Pompe disease
d) Glycosaminoglycans – Mucopolysaccharidoses

The clinical manifestations of some lysosomal storage diseases are very similar, and they resemble other developmental and neurological disorders. Therefore, the diagnosis of a specific lysosomal storage disease requires a combination of clinical, morphological, biochemical, and molecular biological techniques. Foamy transformation of macrophages is typically seen in lysosomal storage disorders in patients with Niemann-Pick disease and Gaucher cells.[6]

Niemann-Pick disease type A (NPA) and type B (NPB) refer to two related diseases that are characterized by lysosomal accumulation of sphingomyelin resulting from an inherited deficiency of sphingomyelinase. Sphingomyelin is an ubiquitous component of cellular (including organellar) membranes, and so the enzyme deficiency blocks degradation of the lipid, resulting in its progressive accumulation within lysosomes, particularly within cells of the mononuclear phagocyte system. Affected cells become enlarged, sometimes to 90 μm in diameter, secondary to the distention of lysosomes with sphingomyelin and cholesterol. Innumerable small vacuoles of relatively uniform size are created, imparting a foaminess to the cytoplasm. The lipid-laden macrophages (phagocytic foam cells) are widely distributed in the spleen, liver, lymph nodes, bone marrow, tonsils, gastrointestinal tract, and lungs.[7]

Tuberculosis

Tuberculosis (TB) is a chronic inflammatory disease caused by a Mycobacterium tuberculosis (Mtb). Once the bacilli are inhaled, alveolar and interstitial macrophages become infected with Mtb and differentiate into lipid-laden foamy macrophages leading to lung inflammation. Thus, the presence of lipid-laden foamy macrophages is the hallmark of TB granuloma; these Mtb-infected foamy macrophages are the major niche for Mtb survival. The fate of TB pathogenesis is likely determined by the altered function of Mtb-infected macrophages, which initiate and mediate TB-related lung inflammation. As Mtb-infected foamy macrophages play central roles in the pathogenesis of Mtb, they may be important in the development of host-directed therapy against TB.[8]

Chlamydia

Chlamydiae are obligate, intracellular bacteria that have a biphasic developmental cycle. The cells infected by Chlamydia include epithelial cells, smooth muscle cells, fibroblasts, osteoblasts, monocytes/macrophages and dendritic cells.The two major chlamydial species that are pathogenic to humans are Chlamydia trachomatis and Chlamydia pneumoniae.[9] Infection with C.trachomatis can lead to non-congenital blindness and genital tract infections and complications such as pelvic inflammatory disease, infertility, ectopic pregnancy, urethritis and cervical cancer. C. pneumoniae causes respiratory infections including pneumonia, bronchitis, pharyngitis and sinusitis. C. pneumoniae has also been linked to asthma, arthritis, atherosclerosis, stroke, multiple sclerosis and Alzheimer›s disease.

An oral reservoir of C. pneumoniae could infect circulating immune cells and thus contribute to other inflammatory diseases. This could be the cause for atherosclerosis, since individuals with periodontitis are known to be at a higher risk for foam cell formation and arteriosclerosis.[10]

Xanthogranulomatous

Xanthogranulomatous inflammation is a rare form of chronic inflammation, characterized by the presence of lipid-laden macrophages admixed with lymphocytes, plasma cells, neutrophils, and multinucleated giant cells. Etiology of xanthogranulomatous inflammation is uncertain. It has been reported in different organs, such as gall bladder, urinary bladder, kidney, and others.

Only one case has been reported with gingival involvement. A case with xanthogranulomatous inflammation of gingiva in site of extracted 36 the tooth presented with focal gingival enlargement of a 20yr old woman. Surgical excision was performed for therapeutic and diagnostic purposes. Macroscopically, the specimen was 12x8x5 mm in size, unilaterally mucosa-covered, white-yellow colored in section surface. Histopathologically, abundant collagen fibers and fibroblasts were seen in specimen. Large number of lymphocytes and plasma cells, small foci of foamy macrophages and degenerative calcification were identified within connective tissue. The specimen was reported as focal fibrous hyperplasia with xanthogranulomatous inflammation and degenerative calcification.[11]

Mucocele

Oral mucocele is a common salivary gland lesion and it occurs most commonly in the lower lips as it is more prone to trauma due to its anatomical location. Trauma is the most common cause of mucous extravasation phenomenon which leads to severance of the salivary duct and spillage of the mucin into the adjoining connective tissue. The spillage of mucin into the connective tissue in turn initiates an inflammatory reaction resulting in the formation of a cystlike cavity lined by granulation tissue wall containing abundant foamy macrophages (containing phagocytosed mucin).[16] (Figure 3)

Radicular cyst

Radicular cysts are the most common inflammatory odontogenic cysts of jaws. They are found mostly at the apices of the tooth (periapical cyst), lateral surface of the roots (lateral radicular cyst) and remains in the jaw after removal of the offending tooth (residual cyst). The pathogenesis involves the activation of the epithelial remnants in the periodontal ligament which occurs as a result of inflammation.

Histopathologically, the cystic lining is stratified squamous epithelium with Rushton's hyaline bodies. The fibrous capsule is composed mainly of condensed parallel bundles of collagen fibres peripherally and a loose connective tissue adjacent to epithelial lining. Slow accumulation and deposition of cholesterol during the inflammatory process leads to the formation of "clefts" with acute and chronic inflammatory cells in the connective tissue. Macrophages are involved in the innate phagocytizing response and the acquired response. When they phagocytize cholesterol crystals, they are called foamy macrophages. Thus, the presence of lipid-laden macrophages or foam cells indicate cholesterol-removing mechanism in this lesion.[12] [Figure 1]

Xanthomas

Xanthomas are well circumscribed lesions in the connective tissue of the skin, tendons or fasciae that predominantly consist of foam cells. Foam cells are formed from macrophages as a consequence of gradual intracellular accumulation of lipids taken up by specific receptors or by the mechanism of phagocytosis. The clinical picture of xanthomas is variable, from soft to semisolid skin macules or papules to large nodules, usually of a yellow colour (Greek xanthos = yellow), due to the presence of carotene contained in lipids. Pathogenetic mechanisms involved in the development of xanthomas resemble early stages of atherogenesis. In clinical practice, xanthomas can signalise various congenital or acquired dyslipidemias. The most prevalent form of xanthomas is xanthelasma palpebrarum. Tendinous and tuberous xanthomas are typical for autosomal dominant hypercholesterolemia, as well as for some rare conditions, such as cerebrotendinous xanthomatosis and familial β-sitosterolemia. In patients with familial hypercholesterolemia, the presence of tendinous xanthomas has been shown to be associated with a two to four times higher risk for cardiovascular disease. Eruptive xanthomas are skin manifestations of a severe hypertriglyceridemia and implicate an elevated risk for acute pancreatitis or type 2 diabetes mellitus. Xanthoma stria-

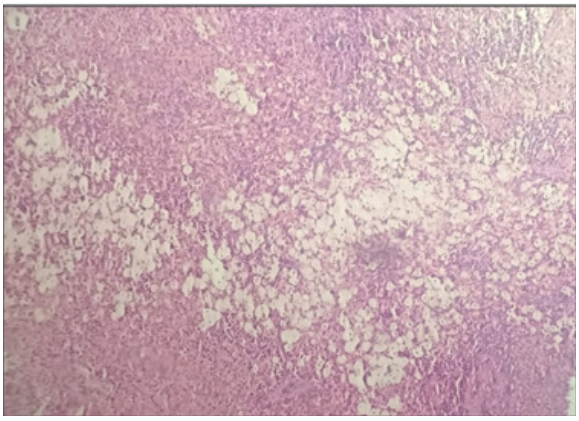

Fig. 1: Foamy macrophages in periapical granuloma

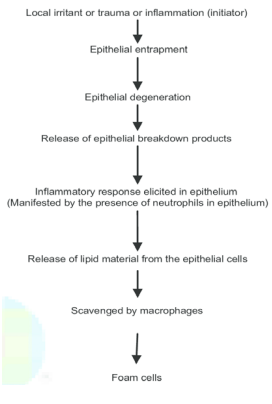

Fig. 2: Flowchart showing etiopathogenesis of verruciform xanthoma [Adapted from [14]

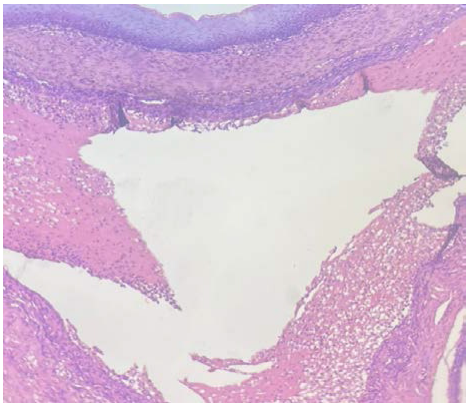

Fig. 3: Mucocele exhibiting mucin and foamy macrophages Hand E,10x

tum palmare is pathognomic for primary dysbetalipoproteinemia, whereas diffuse plane xanthomas are frequently associated with paraproteinemia and lymphoproliferative disorders.[13]

Verruciform xanthoma

Verruciform xanthoma is a very uncommon papillary growth seen chiefly in the oral mucosa. The presence of foam cells in the connective tissue papillae between the epithelial rete ridges forms the hallmark in its diagnosis. Verruciform xanthoma is a relatively uncommon hyperplastic condition of the epithelium affecting primarily the oral mucosa. Gingiva, alveolar mucosa and hard palate are the most common intraoral sites of its occurrence.[5] It usually presents as a solitary, sessile or pedunculated lesion with rough or pebbly surface. It is generally asymptomatic and is about 2 mm-1.5 cm in size with a normal/pale/white/red color. It is reported to occur in adults between 40 and 70 years.

The presence of foamy histiocytes within the elongated dermal papillae forms the hallmark of histopathologic diagnosis of verruciform xanthoma, the nature and origin of these foam/xanthoma cells are debatable even today. Various pathogenic mechanisms are put forth to explain the presence of xanthoma cells in verruciform xanthoma. The latest concept in its etiopathogenesis is an immune mechanism to local trauma or inflammation. The immunohistochemical studies have shown that the predominant cells in the inflammatory infiltrate are T cells.The foam cells are thought to be of monocyte/macrophage lineage, since they are positive to CD68 antibody

It has been reported that the squamous epithelia are active sites of lipid biosynthesis and there is an increase in epidermal lipids in chronic inflammatory dermatoses including verruciform xanthoma. The ultrastructural findings of membrane bound vacuoles in keratinocytes and foamy macrophages in epithelium of verruciform xanthoma further support that the lipids are epithelial origin.

The activated T-lymphocytes due to chronic inflammation recruit macrophages with CCR2 molecules, which in turn upregulates the expression of macrophage scavenger receptor (MSR) on them. These macrophages recognize, trap and internalize the low density lipoproteins (LDL) from the epithelial cells and oxidize it resulting in foam cells. The foam cells express MSR-1 and Ox (oxidized)-LDL. MSR-1 helps in self-sustenance of the long lasting verruciform xanthoma and Ox-LDL acts as a chemoattractant for macrophages and T-cells. According to Zegarelli et al., inflammation due to local irritant or trauma initiates the development of verruciform xanthoma.[14] [Figure 2]

Central xanthoma

Central xanthoma of the jaws is a benign, slowly progressing lesion of activated macrophages containing foamy cytoplasm. It may be infiltrative within marrow spaces. The lesion is capable of considerable destruction of the jaw and may cause bony expansion. It usually occurs in adults in a wide age range. There is a male predilection, and most lesions occur in the mandible. The lesion is treated with curettage, and recurrence has not as yet been reported. Spontaneous resolution has not yet been observed.[15]

Conclusion

"Foamy macrophages" are a common feature of chronic inflammatory process. The presence of these characteristic cells contributes a pathognomonic diagnostic feature in certain oral lesions such as verruciform xanthoma. "Foamy macrophages" play a crucial role in both pathogenesis and diagnosis of oral lesions. Hence, a basic understanding of its formation and role in pathogenesis and diagnosis of certain oral lesions is essential.

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