

Histopathologic Bodies as Diagnostic Clues in Oral Biopsies: A Narrative Review

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Abstract

Histopathologic bodies are abnormal intracellular or extracellular accumulations that serve as crucial diagnostic markers in oral biopsies. This narrative review summarizes various histopathologic bodies identifiable by light microscopy with hematoxylin–eosin (H&E) staining, excluding foreign bodies. These structures are categorized according to their occurrence in inflammatory/granulomatous (e.g., Toto, Rushton, and Russell bodies), immune-mediated (e.g., Civatte and tingible bodies), infectious (e.g., fruiting, mitosoid, and molluscum bodies), and neoplastic (e.g., Verocay, psammoma, and Kamino bodies) conditions of the oral cavity. Familiarity with their microscopic morphology and associated diseases is essential for oral and maxillofacial pathologists to ensure accurate diagnosis.

Keywords: Cell body, Inclusion bodies, Oral, Pathology.

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1. Introduction

The histopathological analysis of tissue involves a comprehensive examination of cellular and nuclear structures and their altered configurations in specific pathologies. This is conducted through a wide range of staining techniques and various microscopic methods. An intriguing aspect is the identification of distinct histopathological bodies associated with various diseases. The identification of these histopathological bodies often serves as a crucial diagnostic marker for determining the underlying condition (1).

Histopathologic bodies are abnormal intracellular or extracellular accumulations that are specifically formed in certain diseases. These structures may be located in the nucleus, cytoplasm, or both (2). Inclusion bodies arise from disruptions in the body's normal homeostasis, and their presence often indicates an underlying disease. Moreover, these structures may result from cellular or nuclear alterations triggered by biochemical changes occurring during the course of the disease, serving as a significant diagnostic characteristic for various pathological conditions (3).

Histopathological bodies can be classified into physiological and pathological categories. The latter includes infections (viral, bacterial, and fungal), cysts, neoplasms, autoimmune

diseases, blood dyscrasias, and inflammatory conditions (1,2,4). Moreover, foreign bodies represent a highly diverse group, encompassing substances such as cosmetic fillers, dental materials, and plant-derived matter, all of which may be considered as histopathological bodies (5-7).

Some of the histopathologic bodies, including Odland, Weibel–Palade, and Birbeck bodies, are identifiable only by electron microscopy (8), whereas others can be observed with a light microscope.

Certain histopathologic bodies have been described in organs beyond the oral cavity, including Negri bodies, Heinz bodies, and others (9,10). This review focuses exclusively on histopathologic bodies identifiable in oral biopsy specimens by light microscopy with hematoxylin–eosin (H&E) staining and discusses their etiopathogenesis, excluding foreign bodies owing to their considerable variability.

2. Search strategy

General search engines and specialized databases, including PubMed, PubMed Central, Scopus, and authenticated textbooks, were used to find relevant articles by means of keywords such as “Oral Pathology”, “Histopathologic Body”, and “Cell Body”. Based on the obtained literature, this

narrative review summarizes various histopathologic bodies identifiable by light microscopy with hematoxylin–eosin staining, categorized according to their occurrence in inflammatory, immune-mediated, infectious, and neoplastic conditions.

3. Histopathologic bodies found in the inflammatory process/granulomatous condition

3.1. Toto body

These are eosinophilic bodies of homogeneous masses that conform in size and shape, predominantly found in the superficial spinous layer of the surface epithelium and are referred to as “Mucopolysaccharide Keratin Dystrophy” (Figure 1A) (11). They are usually round to oval in shape with a peripheral clear appearance (12) and are seen in inflammatory lesions of the gingiva and other mucosal sites, such as pyogenic granuloma, epulis fissuratum, irritation fibroma, peripheral giant cell granuloma, and inflammatory hyperplastic gingivitis (11,12). Toto body is positive for periodic acid-Schiff (PAS) and alcian blue (11). Keratin-like materials or blood plasma infiltrates have been proposed as the origin of this structure. These structures are believed to result from the accumulation of glycoproteins, mucopolysaccharides from the normal intercellular substance, and plasma fluid secretions within the dilated intercellular spaces of degenerating surface cells (13). Gowsalya et al. (12) found a positive correlation between the presence of epithelial Toto bodies and inflammation in the underlying connective tissue, suggesting that their presence may serve as a diagnostic indicator of the lesion’s reactive or inflammatory nature.

3.2. Rushton body (Hyaline body)

These structures present as eosinophilic, glassy bodies with straight, curved, irregular, rounded, or polycyclic shapes, occurring at variable frequencies in the epithelial lining of odontogenic cysts. (Figure 1B) (14). The most common cysts that exhibit this structure include radicular cyst, dentigerous cyst, and odontogenic keratocyst, respectively. Several theories have been proposed, suggesting either an odontogenic epithelial or hematologic origin (15), with some studies supporting both (16) and others refuting either (17).

3.3. Russell body

These are eosinophilic, homogeneous inclusions composed of immunoglobulins, typically found in plasma cells undergoing excessive immunoglobulin synthesis (Figure 1C). Special stains such as fuchsin, periodic acid-Schiff, and Grunwald-Giemsa stain are used to demonstrate Russell bodies. Russell body formation is thought to result from defective clearance of misfolded or improperly assembled proteins, leading to cellular indigestion. They are commonly observed in periapical granuloma/cyst, multiple myeloma/plasmacytoma, and *Helicobacter pylori* infection (2).

3.4. Giant cell hyalin angiopathy (oral pulse granuloma/ hyaline body)

It can be found in soft tissue and cyst walls, characterized by hyaline rings surrounded by multinucleated giant cells. The lesion features fibrosis, mature fibroblasts, vacuolated macrophages, plasma cells, and lymphocytes (Figure 1D). There are two main hypotheses regarding its pathogenesis. First, the endogenous theory, which suggests that hyaline rings result from degenerative changes in blood vessels. Second, the exogenous theory, which posits that foreign food particles trigger a reaction, forming hyaline rings in areas like extraction sockets and periodontal pockets. The fibrillar material in the rings may be collagen (18).

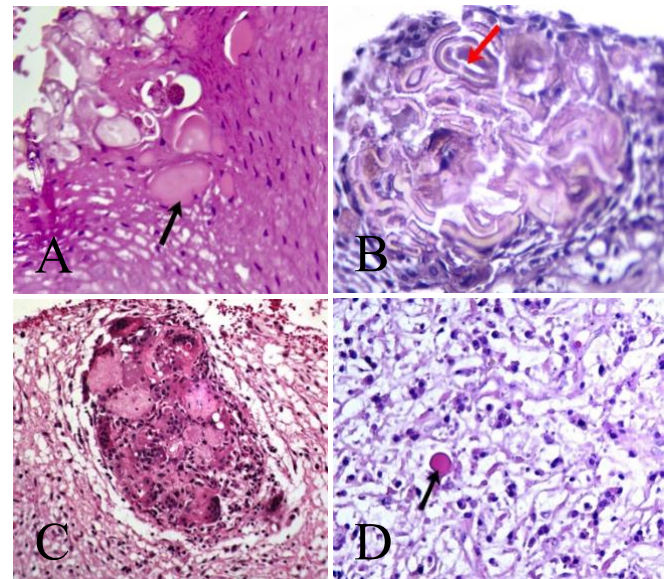


Figure 1. A) Toto body. The black arrow shows eosinophilic material in the superficial epithelium of a pyogenic granuloma (H&E, ×400). B) Rushton body. The black arrow shows curved and irregular glassy structures occurring within the epithelium of the periapical cyst (H&E, ×400). C) Giant cell hyaline angiopathy. Hyaline rings surrounded by multinucleated giant cells in the fibrous wall of a periapical cyst (H&E, ×100). D) Russell body. The black arrow displays an eosinophilic globule of gamma globulin in an inflammatory cyst wall (H&E, ×400).

3.5. Schaumann (Conchoidal) body

Large basophilic concentric lamellar calcifications frequently comprising central birefringent calcium oxalate crystals. They are found in sarcoidosis and other granulomatous disorders (Figure 2A) (3,19).

3.6. Hamazaki-Wesenberg (H-W) body

They are oval or spindle-shaped yellow-brown bodies that are seen in sarcoidosis. The pigment appears to be lipofuscin. Ultrastructural studies show that these bodies are giant lysosomes and residual bodies that are acid-fast and stain

positively with silver. However, H–W bodies may be mistaken for budding yeasts when silver staining is used (3).

3.7. Asteroid body

These typically appear as stellate inclusions with multiple rays radiating from a central core within giant cells and may be observed in sarcoidosis. These bodies are entrapped fragments of collagen. They are not specific for sarcoidosis (Figure 2B) (20).

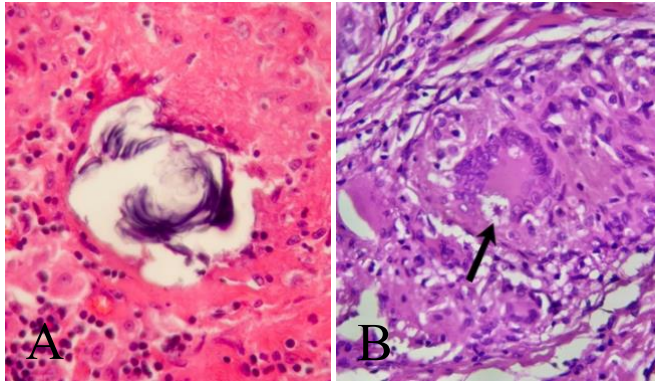


Figure 2. A) Schaumann body. A basophilic concentric lamellar calcification in a granuloma of sarcoidosis (H&E, ×400). B) Asteroid body. The black arrow shows a stellate inclusion in the cytoplasm of a giant cell (H&E, ×400).

4. Histopathologic bodies found in immune-mediated disorders

4.1. Civatte (Colloid) body

They appear as round, homogeneous, eosinophilic masses located in the deeper layers of the epithelium and more frequently within the connective tissue, usually situated within or above the inflammatory cell infiltrate (Figure 3A). These structures are also referred to as colloid bodies, cytoid bodies, hyaline bodies, or Sabouraud bodies (3). Their origin is believed to be damaged basal keratinocytes undergoing apoptotic cell death. They consist primarily of keratin intermediate filaments and are almost invariably coated with immunoglobulins, predominantly IgM (3). They may be observed in lichen planus (LP), discoid lupus erythematosus (DLE), graft-versus-host disease (GVHD), and drug-induced reactions (3,8).

4.2. Tingible body

Tingible body macrophages are mainly seen in germinal centers of lymph nodes. They contain many phagocytized, apoptotic cells in various states of degradation. They engulf nuclear debris from proliferating lymphocytes and can be found in lymphoid hyperplasia and malignant lymphomas (Figure 3B). These lymphocytes have a very high turnover rate; the close macrophages get filled with cellular debris. They are found scattered between proliferating centroblasts,

giving the classic starry-sky pattern. The adjacent neoplastic lymphocytes, or normal lymphocytes within reactive lymph nodes, possess scant cytoplasm and dark nuclei, creating a dark blue background often described as the “sky” (21).

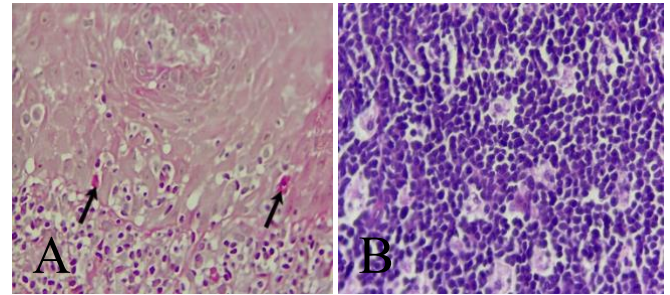


Figure 3. A) Civatte body. Black arrows show homogeneous and eosinophilic masses located in the deeper layers of the epithelium (H&E, ×400). B) Tingible body. Macrophages engulf nuclear debris from proliferating lymphocytes in Burkitt lymphoma (H&E, ×400).

5. Histopathologic bodies found in infections

5.1. Fruiting body

Noninvasive forms of aspergillosis exhibit histopathological features that differ from those of invasive aspergillosis. For instance, a fungal ball is characterized by a tangled mass of hyphae with no signs of tissue invasion. Since the fungal ball develops in a paranasal sinus, where it is exposed to air, it produces spore-bearing structures known as fruiting bodies (22).

5.2. Mitosoid body

These structures are often located within the middle spinous layer of the epithelium. Their nuclei exhibit fragmented DNA and coarse clumping of heterochromatin, giving them an appearance like that of mitotic figures (3). They are considered hallmarks of focal epithelial hyperplasia, a condition associated with human papillomavirus (HPV) infection, particularly types 13, 32, or both (3,23,24).

5.3. Molluscum body (Henderson Paterson body)

They appear as large, round, pink to red, homogeneous intracytoplasmic inclusions located in the stratum spinosum and stratum corneum (Figure 4) (1,3). As the infected cells migrate toward the surface, they may enlarge, and at the granular layer, their staining characteristics shift from eosinophilic to basophilic (3). These bodies consist of nuclear and cytoplasmic aggregates of proteins and represent the sites of viral replication within infected cells (1). Ultrastructural studies reveal that these bodies contain brick-shaped viruses with dumbbell-shaped nucleoids surrounded by an amorphous

capsid layer (3). They could be observed in molluscum contagiosum, a viral infection caused by the Poxvirus group (1).

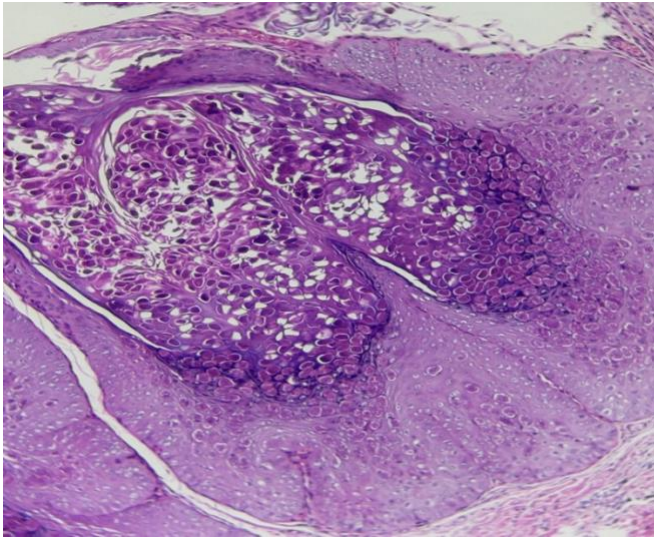


Figure 4. Molluscum body. Large, round, pink to red, homogeneous intracytoplasmic inclusions located in the stratum spinosum (H&E, $\times 100$).

5.4 Warthin–Finkeldey body

They are a type of multinucleated giant cell characterized by large, grape-shaped clusters of nuclei found in hyperplastic lymph nodes (3). These cells express follicular dendritic cell markers and may contain up to 50 nuclei, many of which exhibit intranuclear inclusions (25). Intracytoplasmic hyaline-like inclusions may also be present (3). These may originate from the fusion of follicular dendritic cells (25). They may be observed in the early stages of measles, acquired immunodeficiency syndrome (AIDS), and Kimura disease. Moreover, they are less commonly seen in various neoplastic (lymphoma) and non-neoplastic lymph node disorders (3).

5.5. Cowdry bodies (type I and II)

Cowdry type I bodies are droplet-like masses of acidophilic material surrounded by clear halos located within the nuclei. The nuclei also display changes such as chromatin margination at the nuclear membrane. Cowdry type II bodies resemble type I bodies in appearance, but they do not cause any additional nuclear changes. Type I bodies are associated with herpes infections, while type II bodies are linked to poliovirus infections (2).

5.6. Owl’s eye inclusion bodies

They are found in Hodgkin’s lymphoma and cytomegalovirus (CMV) infections. CMV induces cytopathic effects in the affected cells, leading to the formation of basophilic nuclear inclusions. There is a detectable margination of the chromatin around the nuclear inclusions, resulting in a halo effect or the owl’s eye figure (1,3).

6. Histopathologic bodies found in neoplasms

6.1. Verocay body

It is characterized by a stacked arrangement of two rows of elongated, palisading nuclei alternating with acellular zones composed of Schwann cell cytoplasmic processes (Figure 5a). Their prominent formation in epithelial adnexal tumors is referred to as the “rippled pattern”. They result from the overexpression of laminins, leading to the alignment of nuclei into compact rows separated by intervening acellular material. They are identifiable in schwannomas and various cutaneous neoplasms (26).

6.2. Psammoma Body

They are round, basophilic, concentrically lamellated calcified structures containing mineralized collagenous foci (27). Their size and shape vary from small, smooth, round or oval forms to larger, irregular ossicle-like patterns (3). These structures are commonly believed to result from dystrophic calcification. Ultrastructural studies suggest that they form following thickening of the basal lamina in the vascular stalks of neoplastic papillae, followed by thrombosis, calcification, and tumor cell necrosis. However, they may also represent an active biological process that ultimately contributes to the growth retardation of the neoplasm (27). They may be observed in papillary thyroid carcinoma (PTC), meningioma, papillary serous cystadenocarcinoma, psammomatoid melanotic schwannoma, and juvenile ossifying fibroma (27,28).

6.3. Wagner Meissner body

These are tactile corpuscle-like oval aggregates of eosinophilic globules containing parallel slits and bordered by nuclei, typically found in neurofibromas (3). Furthermore, they may also be observed in schwannomas and cellular nevi (29).

6.4. Kamino Body

These typically appear as dull pink, solitary, confluent, or rounded amorphous eosinophilic globules with scalloped margins, located at the dermoepidermal junction above the tips of the dermal papillae (30,31). They can be stained with trichrome in a manner similar to collagen fibers (30). Additionally, their eosinophilic appearance may be masked by melanin pigmentation (31). It has been reported that the globules are composed of basement membrane material, including type IV and VII collagen as well as laminin (30). They are identifiable in Spitz nevus, Reed nevus, Spitzoid tumors, and malignant melanoma (31).

6.5. Pustulo-ovoid Bodies of Milian

The granular cell tumors are characterized by large cells with centrally placed nuclei, eosinophilic granular cytoplasm, and variable pseudoepitheliomatous hyperplasia (32). On high-power microscopic examination, granular cell tumors also display large, round eosinophilic granules surrounded by a clear halo, measuring approximately 4–5 mm in size. These structures have been called the pustulo-ovoid bodies of Milian. They result from the progressive accumulation within individual lysosomes, with more mature tumors predicted to exhibit a higher frequency of larger granules (33).

6.6. Crystalloids

These can occur in salivary gland tumors such as pleomorphic adenoma, presenting in two distinct forms. The tyrosine-rich variant was characterized by radially arranged, petal-shaped clusters of glossy, eosinophilic material encircling a central core. The peripheral projections displayed a distinctly lobulated contour, and the structures appeared refractile upon in-and-out focusing. However, the collagen-rich variant consisted of radially arranged clusters of eosinophilic, needle-shaped fibers. Centrally, a clear space was often present, occasionally containing one or more elongated cells of apparent connective tissue origin or a thin-walled blood vessel. The fiber tips were pointed and lacked refractility upon in-and-out focusing (Figure 5A) (34,35).

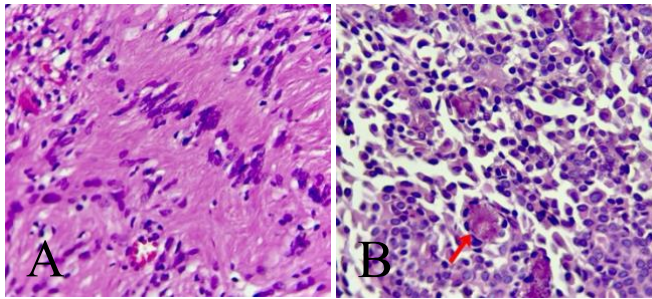


Figure 5. A) Verocay body. The Schwann cells of the Antoni A tissue form a palisaded arrangement around an acellular zone (Verocay bodies) (H&E, $\times 400$). B) Crystalloids. Radially arranged clusters of eosinophilic, needle-shaped fibers in pleomorphic adenoma rich in plasmacytoid cells (H&E, $\times 400$).

6.7. Dutcher bodies

They are found in neoplastic plasma or plasmacytoid cells, occurring in multiple myeloma as well as other B-cell neoplasms. Dutcher bodies and Russell bodies are intracytoplasmic spherical inclusions of similar origin. Dutcher bodies invaginate into or overlie the nucleus, while Russell bodies are distinctly observed within the cytoplasm (36).

7. Conclusion

This narrative review summarizes the wide spectrum of histopathologic bodies encountered in oral biopsy specimens, along with their associated diseases or lesions, microscopic morphology, and possible etiologies. Identifying these microscopic structures may serve as an important clue for accurate diagnosis. Therefore, familiarity with these structures is indispensable for oral and maxillofacial pathologists.

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Ethics

Not applicable.

Using artificial intelligence (AI)

The authors used ChatGPT (OpenAI) to improve the language fluency of the text. However, the authors thoroughly reviewed the manuscript and took full responsibility for the final version of it.

Author contributions

Melika Namvar: Writing – Original draft, Investigation, Data curation, Visualization

Saede Attarbashi-Moghadam.: Writing – Review & editing, Conceptualization, Supervision, Investigation

Bahram Ardalani: Validation, Methodology, Project administration, Methodology, Supervision

Mohammadreza Kashefi Bahar: Writing – Original draft, Writing – Review & editing, Visualization, Data curation, Investigation, Supervision.

Conflict of interest

All authors have no conflicts of interest to disclose.

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