Non-microbial etiology: periapical cysts sustain post-treatment apical periodontitis

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IN MICROSCOPY, AS IN NATURE, ONE RECOGNIZES ONLY WHAT ONE ALREADY KNOWS. Routine histopathological diagnostic reports and publications based on retrospective reviewing of such, perpetuate the notion that nearly half of all apical periodontitis lesions are cysts. Studies based on meticulous serial sectioning of apical lesions retrieved *in toto* show that the actual prevalence of cysts is only about 15% of all apical periodontitis lesions. Periapical cysts exist in two structurally distinct classes, namely those containing cavities *completely enclosed in epithelial lining* (periapical true cysts) and those containing epithelium-lined *cavities that are open to the root canals* (*periapical pocket cysts*). From a clinical point of view, small cysts, particularly the pocket cysts, can heal after non-surgical root canal therapy whereas large cysts, mainly true cysts, are less likely to be resolved without surgical intervention.

Introduction

There is an evolving consensus that the cause of posttreatment apical periodontitis associated with welltreated root-filled teeth is the *microbial infection* (1-4)persisting in the complex, apical root canal system (5, 6). The infection cannot be fully eradicated by existing instruments, techniques and medicaments. Certain other etiological factors located beyond the root canal system, within the inflamed periapical tissue, also cause post-treatment apical periodontitis but their prevalence is much lower than that of root canal infection. These factors include extraradicular actinomycotic infections (7-10), foreign body reaction to exogenous materials (11) or endogenous cholesterol crystals and a cystic condition of the lesion (12). These factors are reviewed in other articles in this issue. This article is meant to provide a comprehensive overview of the pathobiology of periapical cysts, the problem of cyst diagnosis and the lingering controversy regarding the ability of a periapical cyst to heal after non-surgical root canal treatment.

Periapical cyst

A cyst is a closed pathological cavity, lined by an epithelium that contains a liquid or semisolid material (13). The term cyst is derived from the Greek *Kystis*

meaning sac or bladder. There are diverse cystic lesions in the human body that are commonly categorized as congenital, neoplastic, parasitic, retention, implantation and inflammatory types. Periapical cysts are inflammatory jaw cysts at the apices of teeth with infected and necrotic pulps.

Incidence

The epidemiological prevalence and geographical distribution of the disease are not yet known. Periapical cysts are the most common of all jaw cysts and comprise about 52% (14) to 68% (15) of all the cysts affecting the human jaws. Their prevalence is highest among patients in their third decade of life (14, 16, 17), and higher among men than women (14, 16). Anatomically, the apical cysts occur in all tooth-bearing sites of the jaws but are more frequent in maxillary than mandibular teeth. In the maxilla, the anterior region appears to be more prone to cyst development whereas in the mandible the radicular cysts occur more frequently in the premolar region (18).

Diagnosis of cysts

The differential diagnosis of cysts from other forms of apical periodontitis lesions has been extensively

debated over the years (19). Several radiographic features have been proposed to support a diagnosis, including size of the lesion and the presence of a radioopaque rim demarcating the lesion. Although the statistical probability of cyst occurrence may be higher among larger lesions (20), a definite relationship between lesion size and cystic condition has not been supported by histology. Contrary to a claim (21), periapical lesions cannot be differentially diagnosed into cystic and non-cystic lesions based on conventional radiographs (16, 22-26). Assuming that cystic cavities may have a lower density than other apical periodontitis lesions, computer tomography (27) and densitometry (21) have been used to differentiate these conditions, but without success. Ultrasonic imaging technique (echography) has been recently introduced as a periapical diagnostic method (28, 29). The technique seems to be useful in detecting fluid, soft tissue and the real-time blood flow. In spite of the safety of ultrasound and the relative ease of use, the sonic waves do not pass through bone but are reflected back to the sensor, thereby enabling only detection of lesions that are not enclosed in bone. Currently, therefore, histological serial sectioning of the lesions in toto remains to be the only reliable diagnostic method of periapical cysts (30, 31). This, however, can only be applied after surgical removal of the root tip and periapical lesion; thus, it is a post hoc diagnosis.

The cyst epithelium

Apical periodontitis lesions often contain epithelial cells (32-43) that are believed to be derived from the cell rests of Malassez (32). They proliferate in some lesions and are presumed to serve as the major source of the stratified squamous epithelium (14, 31) that lines the lumen of lesions that develop into cysts. Rarely, however, periapical cysts have also been found to be lined partially or predominantly by ciliated columnar or muco-secretory cells that have respiratory origin (43-51). In a recent investigation (51), three of the 256 apical periodontitis lesions examined were cysts lined with ciliated columnar epithelium (Figs 1 and 2). However, the origin of ciliated epithelium in radicular cysts has not yet been satisfactorily clarified. There have been three explanations (48) for the presence of ciliated cells in radicular cysts: (i) migration of such cells from the maxillary sinus or the nasal cavity, (ii) metaplasia of the stratified squamous epithelium and (ii) differentiation of pluripotent cells within the jaw. Most of the reported ciliated cell-lined cysts were affecting maxillary teeth. The close anatomical proximity of the inflammatory lesion to the maxillary sinus may result in rarefaction of the sinus floor and perforation into the sinus cavity (43, 45). Such periapical inflammation has been reported to cause maxillary sinusitis (52–54). The lumen of a periapical cyst in the region may even communicate with the sinus cavity as has been convincingly demonstrated in photomicrographs by Kronfeld (45). Once direct communication is established, a developing periapical cyst may become lined partially or completely with ciliary epithelium of sinus origin.

Prevalence among periapical lesions

There have been many studies on the prevalence of periapical cysts among apical periodontitis lesions (Table 1). In this literature, the prevalence of cysts varies from 6% to 55%. However, accurate histopathological diagnosis of radicular cysts is possible only through serial sectioning or step-serial sectioning of the lesions removed in toto (30). There are only three studies (30, 36, 55) in which either one of those essential techniques was used, while most of the others (Table 1) analyzed specimens obtained from wide sources for routine histopathological reports. The statistically impressive 2308 lesions in Bhaskar's study (16) had been obtained from 314 contributors and the 800 biopsies of Lalonde and Luebke (26) originated from 134 sources. Such histopathological diagnostic specimens, often derived through apical curettage, do not represent lesions in toto. In random sections from fragmented and epithelialized lesions, part of the specimens can give the appearance of epithelium-lined cavities that do not exist in reality. Indeed, other authors (56) defined a typical radicular cyst as one in which 'a real or imagined lumen was lined with stratified squamous epithelium'.

It should be pointed out that the photomicrographic illustrations (Fig. 3) in several studies (16, 26) represent only magnified views of selected small segments of epithelialized lesions. They are not supported by overview pictures of lesser magnifications of sequential sections derived from different axial planes of the lesions in question. The wide variation in the reported incidence of periapical cysts is most



Fig. 1. A photomicrograph (a) of a cystic apical periodontitis (AP) of the left maxillary second premolar of a 34-year-old male patient. Note the two diverticula of a small cystic lumen magnified in (b) and part of the epithelial lining enlarged in (c). The lumen (LU) is lined with columnar epithelial cells (CEP) with distinct cilia (arrow heads). D, dentine. Original magnifications: (a) \times 19; (b) \times 44; (c) \times 500. From (51). Reproduced with permission.



Fig. 2. A transmission electron micrograph of ciliated columnar epithelial cells (CEP) lining of the cystic lumen of the lesion presented in Fig. 1. Note the distinct cilia (CI) and the neutrophilic gametocytes (NG). FI, fibroblasts. Original magnification \times 3690. From (51). Reproduced with permission.

Reference	Cysts (%)	Granuloma (%)	Others (%)	Total lesions (n)
Somer et al. (82)	6	84	10	170
Block et al. (83)	6	94	-	230
Sonnabend and Oh (36)	7	93	-	237
Winstock (84)	8	83	9	9804
Linenberg et al. (25)	9	80	11	110
Wais (24)	14	84	2	50
Patterson et al. (85)	14	84	2	501
Nair et al. (30)	15	50	35	256
Simon (55)	17	77	6	35
Stockdale and Chandler (86)	17	77	6	1108
Lin et al.(87)	19	-	81	150
Nobuhara & Del Rio (88)	22	59	19	150
Baumann & Rossman (23)	26	74	-	121
Mortensen et al. (17)	41	59	-	396
Bhaskar (16)	42	48	10	2308
Spatafore et al. (89)	42	52	6	1659
Lalonde and Luebke (26)	44	45	11	800
Seltzer et al. (56)	51	45	4	87
Priebe et al. (22)	55	45	-	101

probably due to the difference in the histopathological interpretation of the sections. When the histopathological diagnosis is based on random or limited number of serial sections, most of epithelialized periapical lesions would be wrongly categorized as radicular cysts. This view is strongly supported by the results of a study (30) in which an overall 52% of the lesions (n = 256) were found to be epithelialized, but only 15% were actually periapical cysts.

Histopathogical categories of radicular cysts

The structure of a periapical cyst in relation to the root canal of the affected tooth has not been taken into account in routine histopathological diagnosis. The major reason for this has been the nature of the biopsy itself. Apical specimens removed by curettage do not contain the root tips of the diseased teeth, making structural reference to the root canals of the affected teeth impossible. In 1980, Simon (55) pointed out that there are two distinct categories of radicular cysts, namely those containing cavities completely enclosed in epithelial lining and those containing epithelium-lined cavities that are open to the root canals. The latter was designated as 'bay cysts' (55) and later renamed as 'pocket cysts' (30). It seems that Simon (55) has observed only the large type of such lesions with voluminous cavities, into which the root apices of the affected teeth appeared to protrude. The photomicrographs in the publication reveal severe damage of the



Fig. 3. Roentgenogram (top) and photomicrograph (bottom) of a 'radicular cyst'. Note the small selected segment of an epithelialized lesion. It is not supported by overview pictures of lesser magnification of sequential sections derived from different axial planes of the lesion. From (16). Reproduced with permission from Elsevier.

microanatomical relationship between the root apices and the cyst epithelia (Fig. 4). This might have influenced critics to wonder whether the 'bay cysts' (55) are histological artifacts. We (30) analyzed 256 periapical lesions obtained in toto with extracted teeth. The specimens were processed by a modern plasticembedding technique, and meticulous serial or stepserial sections were prepared and evaluated based on pre-defined histopathological criteria. Out of the 256 specimens, 35% were found to be periapical abscesses, 50% were periapical granulomas, and only 15% were periapical cysts. Equally significant was the finding that two distinct classes of radicular cysts - the apical true cysts, with cavities completely enclosed in epithelial linings (Fig. 5) and the apical pocket cysts, with cystlumina open to the root canals (Fig. 6) – could be observed at the periapex when the lesions were analyzed in relation to the root canals. An overall 9% of the 256 lesions were apical true cysts and 6% were periapical pocket cysts.



Fig. 4. Root apices in cavities lined by epithelium (E in top). Note the severe damage of the micro-anatomical relationship between the root apices and the cyst epithelia that might have influenced critics to wonder whether the 'bay cysts' (55) are histological artifacts. Original magnification \times 25. From (55). Reproduced with permission from Lippincott, Williams & Wilkins.

Pathogenesis of true cysts

The periapical true cyst may be defined as a chronic inflammatory lesion at the periapex that contains an epithelium-lined, *closed pathological cavity* (Fig. 5). The pathogenesis of true cysts has been described by various authors (30, 31, 33, 57–63). An apical cyst is a direct sequel to apical granuloma, although a granuloma need not always develop into a cyst. Due to still unknown reasons only a small fraction (<10%) of the periapical lesions advance into true radicular cysts (16, 26). The pathogenesis of the true cyst has been described in three phases (14). During the *first phase*, the dormant cell rests of Malassez begin to proliferate as a direct effect of inflammation (61, 64), probably under the influence of bacterial antigens (65), epidermal growth factors (66–68), cell mediators and metabolites that are



Fig. 5. Periapical true cyst. Photomicrograph (a) of an axial section passing through the apical foramen (AF). The lower half of the lesion and the epithelium (EP in b) are magnified in (b) and (c), respectively. Note the cystic lumen (LU) with cholesterol clefts (CC) completely enclosed in epithelium (EP) having no communication to the root canal. Original magnifications: (a) $\times 15$; (b) $\times 30$; (c) $\times 180$.



Fig. 6. Periapical pocket cyst. Axial sections passing peripheral to the root canal (a, b) give the false impression of the presence of a cyst lumen (LU) completely enclosed in the epithelium. Sequential section (c) passing through axial plane of the root canal clearly reveals the continuity of the cystic lumen (LU) with the root canal (RC in d). The apical foramen with the cyst lumen (LU) of the section (c) is magnified in (d). Note the pouch-like lumen (LU) of the pocket cyst with the epithelium (EP) forming a collar at the root apex. Original magnifications: (a)–(c) \times 15; (d) \times 50. D, dentine. Adapted from (90). Reproduced with permission.

released by various cells residing in the periapical lesion. During the second phase, an epithelium-lined cavity comes into existence. There are two main theories regarding the formation of the cyst cavity: (i) the 'nutritional deficiency theory' is based on the assumption that the central cells of the epithelial strands become removed from their source of nutrition and undergo necrosis and liquefactive degeneration (61, 69-71). The accumulating products in turn attract neutrophilic granulocytes into the necrotic area. Such microcavities containing degenerating epithelial cells, infiltrating mobile cells and tissue fluid coalesce to form the cyst cavity lined by stratified epithelium, (ii) the 'abscess theory' postulates that the proliferating epithelium lines an abscess cavity formed by tissue necrosis and lysis because of the innate nature of the epithelial cells to cover exposed connective tissue surfaces (34, 38). During the third phase the cyst grows, but whose exact mechanism is still unknown. It is generally believed to be by osmosis. The presence of necrotic tissue in the cyst lumen attracts neutrophilic granulocytes, which extravasate and transmigrate through the epithelial lining (Figs 7 and 8) into the cyst cavity where they perish. The lytic products of the dying cells in the cyst lumen release a greater number of molecules. As a result, the osmotic pressure of the cyst fluid rises to a level higher than that of the tissue fluid (72). The latter diffuses into the cyst cavity so as to raise the intraluminal hydrostatic pressure well above the capillary pressure. The increased intracyst pressure may lead to bone resorption and expansion of the cyst. However, the fact that an apical pocket cyst with lumen open to the necrotic root canal can become larger (30, 63) suggests against osmotic pressure as a potential factor in the development of radicular cysts. Further, there is increasing evidence in support of a molecular mechanism for cyst expansion (63). The T-lymphocytes (73) and macrophages in the cyst wall may provide a continuous source of bone resorptive metabolites (74) and cytokines. The presence of effector molecules such as matrix metalloproteinase-1 and -2 have also been reported in the cyst walls (75).

Fig. 7. Composite transmission electron micrograph showing neutrophils (NG, arrowheads) apparently in the process of transmigration through the epithelial wall of a cyst (EP) into the cyst lumen (LU). ST, subepithelial tissue; PC, plasma cells; MA, macrophages. Original magnification \times 1600. Adapted from (63).





Fig. 8. An intramural scanning electron microscopic view of a cyst luminal wall (LU, in a) enlarged in stages (b–d). Note the flat epithelial cells (EP) and the globular neutrophilic granulocytes (NG). The latter emerge through the interepithelial-cell-spaces into the cyst lumen. Original magnifications: (a) $\times 20$; (b) $\times 230$; (c) $\times 670$; (d) $\times 1300$.



Fig. 9. Overview photomicrograph (a) of an apical periodontitis lesion (AP). The resorbed root-tip with widened apical foramen is magnified in (b). Note the bacterial plaque (white arrow head, BA) at the apical foramen and the microabscess (MA) externalized by an epithelial (EP) ring attached to the root tip. The rectangular demarcated area in (a) is magnified in (c). Note the numerous subepithelial blood vessels (BV) that are further magnified in (d). The bacteria (BA) attract neutrophils (NG) to form the micro-abscess in front of the apical foramen, which probably is the initiation of a periapical pocket cyst. D, dentine. Original magnifications: (a) $\times 20$; (b) $\times 50$; (c) $\times 130$; (d) $\times 310$.



Fig. 10. High-magnification photomicrographs (a–d) of the bacterial plaque (BA) shown in Fig. 9 and the micro-abscess containing clusters of bacterial colonies (BA) apparently held back by a wall of neutrophils (NG). D, dentine; EP, epithelium. Original magnification: (a), (c), (d) \times 800; (b) \times 520.

Pathogenesis of pocket cysts

The periapical pocket cyst contains an epithelium-lined pathological cavity that is open to the root canal of the affected tooth (Fig. 6). As mentioned previously, such lesions were originally described as 'bay cysts' (55). It has been postulated that biologically, a pocket cyst constitutes an extension of the infected root canal space into the periapex. The microluminal space become enclosed in a stratified squamous epithelium that grows and forms an epithelial collar (Fig. 9) around the root tip. The epithelial collar forms an 'epithelial attachment' (42) to the root surface so as to seal off the infected root canal and the micro-cystic lumen from the periapical milieu and the rest of the body (Fig. 9c, d). The presence of microorganisms at the apical foramen (Fig. 10) attracts neutrophilic granulocytes by chemotaxis into the microlumen. However, the pouch-like lumen – biologically outside the body milieu – acts as a 'death trap' to the externalized neutrophils. As the necrotic tissue and microbial products accumulate, the sac-like lumen enlarges to accommodate the debris, forming a voluminous diverticulum of the root canal space into the periapical area (Figs 11 and 12). It has been pointed out (30) that from the pathogenic, structural, tissue dynamic, host-benefit and protection stand points, the epithelium-lined pouch-like extension of the root canal space of such lesions has much in common with a marginal periodontal pocket. This appears to justify the terminology of 'periapical pocket cyst' as opposed to the biologically meaningless term 'bay cyst' (55). In this context, it is interesting to note that cystic lesions with morphological features identical to that of pocket cysts have been histologically



Fig. 11. Photomicrograph of a well-developed pocket cyst (a). Note the sac-like epithelial lumen (LU, enlarged in b). A sequential, axial serial section (c) passing through the apical foramen in the root canal plane (RC) shows the continuity of the lumen to the root canal. D, dentine. Original magnification: (a), (c) $\times 16$; (b), (d) $\times 40$.



Fig. 12. Macrophotographs (a, b) of a large apical periodontitis lesion removed *in toto* by apical surgery (a). The specimen after decalcification and axial subdivision (b) shows a voluminous lumen into which the root canal opens.

illustrated by Seltzer (76) in a text book and also experimentally induced in monkeys by Valderhaug (64, 77). However, these authors neither differentiated nor interpreted the lesions in relation to the root canals of the involved teeth – a reminder that in microscopy, as in nature, one recognizes only what one already knows.

Controversy over the healing of periapical cysts

The occurrence of two distinct classes of radicular cysts and the low prevalence of true cysts (<10%) are both significant considerations in clinical management of primary and particularly post-treatment apical periodontitis. Many clinicians hold the view that cysts do not heal and thus must be removed by surgery. It should be pointed out with emphasis that apical periodontitis lesions cannot be differentially diagnosed into cystic and non-cystic lesions based on radiographs (16, 17, 22–25, 78). However, routine histopathological diagnostic reports and publications based on retrospective reviewing of such have perpetuated the notion that nearly half of all periapical lesions are radicular cysts. As a result, a disproportionately large number of surgical interventions are carried out at the tooth apex to 'enucleate' lesions that are clinically diagnosed as 'cysts'. In fact, studies based on meticulous serial sections have shown that the incidence of *true cysts* is less than 10% of all periapical lesions (30, 36, 55). This would imply that most of the cases in which apical surgery has been performed based on radiographic diagnosis of cysts might have resolved by non-surgical root canal therapy.

The endodontic literature suggests that a great majority of cysts heal after non-surgical root canal therapy. 'Success rates' of 85–90% have been reported (79–81). However, the histological status of any apical radiolucent lesion at the time of treatment is unknown to the clinician, who is also unaware of the differential diagnostic status of the 'successful' and 'failed' cases. Most of the cystic lesions must heal if one should reconcile the high healing rate after non-surgical root canal treatment and the claimed high prevalence of radicular cysts. This conclusion is based purely on a deductive logic in the absence of any histological basis. It must be noted that several investigators listed in Table 1 reached the erroneous conclusion on the high prevalence of cyst based on an incorrect interpretation of epithelialized apical periodontitis lesions.



Fig. 13. Longitudinal radiographs (a–d) of a periapically affected central maxillary incisor of a 37-year-old woman for a period of 4 years and 9 months. Note the large radiolucent asymptomatic lesion before (a), 44 months after root filling (b) and immediately after periapical surgery (c). The periapical area shows distinct bone healing (d) after 1 year post-operatively. Histopathological examination of the surgical specimen by modern tissue processing and step-serial sectioning technique confirmed that the lesion was a true radicular cyst that also contained cholesterol clefts. From (12).

Clinical relevance in primary and post-treatment apical periodontitis

The clinical impact of the structural difference between the apical true cysts and pocket cysts should also be considered. The aim of non-surgical root canal therapy is the elimination of infection from the root canal and the prevention of reinfection by root filling. Periapical pocket cysts, particularly the smaller ones, may heal after root canal therapy (55). The tissue dynamics of a

Reference	Cysts (n)	Granuloma (<i>n</i>)	Scar (<i>n</i>)	Total lesions (<i>n</i>)
Nair et al. (1)	0	9	0	9
Nair et al. (12)	1	0	_	1
Nair et al. (10)	1	3	2	6
Total	2	12	2	16

true cyst is self-sustaining as the lesion is no longer dependent on the presence or absence of root canal infection (30, 55). Therefore, the true cysts, particularly the large ones, are less likely to be resolved by nonsurgical root canal therapy. This has been shown in a long-term radiographic follow-up (Fig. 13) of a case and subsequent histological analysis of the surgical block-biopsy (12). It can be argued that the prevalence of cysts in post-treatment apical periodontitis should be substantially higher than that in primary apical periodontitis. However, this suggestion has not been supported by data based on a statistically reliable number of specimens. Nevertheless, our own investigations (1, 10, 12) of 16 histologically reliable block biopsies of post-treatment apical periodontitis lesions (Table 2) revealed two cystic specimens (13%), possibly true cysts, which is well above the 9% of true cysts observed in a large study (30) on mostly primary apical periodontitis lesions.

Concluding remarks

The existence of two distinct histopathological categories of cystic lesions at the periapex and the low prevalence of periapical cysts would *question the rationale* behind some of the current diagnostic and therapeutic concepts such as: (i) routine histopathological examination of periapical lesions removed by curettage, which does not provide any relevant information but only satisfies certain legal formalities, (ii) disproportionately prevalent application of apical surgery based on unfounded radiographic diagnosis of apical lesions as cysts and (iii) the notion that majority of cysts heal after non-surgical root canal therapy. Nevertheless, clinicians must recognize the fact that the cysts can sustain post-treatment apical periodontitis, and consider the option of apical surgery, particularly when previous attempts at orthograde retreatment have not resulted in healing.

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