Histopathologic Examination to Confirm Diagnosis of Periapical Lesions: A Review

• **Edmund Peters**, DDS, MSc, FRCD(C) •
• **Monica Lau**, DDS, BMedSc •

Abstract

Most periapical lesions are represented by inflammatory cysts, granulomas, abscesses or fibrous scars. These inflammatory conditions are often termed "endodontic lesions" because pulpal necrosis is the initiating event in their pathogenesis. Although rare, other clinically confusing periapical lesions have been extensively documented in numerous case reports and short case series. These lesions represent a wide range of pathosis, including various developmental cysts, infections, benign but locally aggressive lesions, and malignancies. The literature describing these lesions and the value of a histopathologic examination in diagnosis is reviewed.

MeSH Key Words: *jaw neoplasms/pathology; odontogenic cysts/pathology; periapical diseases/pathology*

© J Can Dent Assoc 2003; 69(9):598–600
This article has been peer reviewed.

Periapical lesions resulting from necrotic dental pulp are among the most common pathologic conditions within alveolar bone. Although there are numerous reports of nonendodontic benign or malignant lesions presenting in the periapical area, the large majority are periapical granulomas, cysts or abscesses. As a result, periapical tissue is often submitted for histopathologic review only if there are concerns about the clinical diagnosis, rather than for a routine audit to confirm the clinical diagnosis. The frequency of clinical screening to decide whether biopsy submission is warranted and the extent to which this has an impact on accurate diagnosis are not known. Several studies[1–6] have suggested that between 0.7% to 5.0% of periapical biopsies result in contributory histopathologic findings. However, these studies are almost certainly biased by the previously described clinical selection process. Other histologic studies[7,8] of periapical lesions describing only inflammatory periapical lesions of endodontic origin represent an unresolved inconsistency. This paper reviews and discusses the literature related to histopathologic diagnosis of periapical lesions, with an emphasis on cases showing unusual findings.

Guidelines for Histopathologic Examination

The requirement for histologic examination of periapical tissues in nonhospital settings has received surprisingly little discussion. Several authors[9–13] have recommended that those periapical lesions not responding to conservative endodontic therapy should undergo histopathologic evaluation. The guidelines[14] of the American Association of Endodontists indicate microscopic examination of a periradicular lesion is appropriate any time there is recoverable tissue. However, at least one author,[15] indicating a high level of confidence in the clinical diagnostic process, has argued that careful systematic clinical diagnosis will differentiate endodontic from nonendodontic pathosis and that routine submission of endodontic surgical specimens is of no advantage to the patient. Biopsy submission would, therefore, depend on clinical suspicion. Presumably, from this perspective, the failure to submit periapical tissue in cases that subsequently prove to be of nonendodontic origin would be regarded as an avoidable clinical misdiagnosis.

Retrospective Studies of Periapical Biopsies

Histopathologic diagnoses that identify a pathosis other than periapical granuloma, cyst, abscess or fibrous scar are defined as significant in this discussion. Although these diagnoses are estimated to be between 0.7% and 5.0% of all periapical biopsies,[1–6] no published data describe the frequency with which periapical lesions are submitted for histopathologic examination. Submission of only those selected cases that have caused clinical concern would artificially increase the percentage of periapical biopsies

Table 1 **Cases of unusual periapical pathosis**

Category	Type	No. of cases	References
Cysts	Odontogenic keratocyst	22	3, 4, 9, 17–20
	Nasopalatine duct cyst	4	4, 6, 21, 22
	Lateral periodontal cyst	4	5, 6
	Residual cyst	3	23
	Other[a]	1	3
Infections	Actinomycosis	15	3, 4, 6, 24–34
	Histoplasmosis	1	35
	Aspergillosis	3	6, 36
Benign aggressive lesions	Central giant-cell granuloma	24	1, 4, 6, 9, 13, 37–40
	Other[b]	10	4–6, 10, 41–44
Benign fibro-osseous lesions[c]	Periapical cemental dysplasia	30	1, 4, 45
	Other	2	2, 6
Granulomatous inflammation	Foreign body	40	1, 3–5, 46, 47
	Pulse granuloma	22	48
Malignant lesions	Carcinoma[d]	10	9, 10, 49–55
	Sarcoma	4	10, 44, 56
	Lymphoma	7	4, 10, 44, 57–59
	Other[e]	3	6, 60, 61

[a]*Globulomaxillary cyst: No longer a valid diagnosis.*
[b]*Central ossifying fibroma, 2 myxomas, central odontogenic fibroma, Pindborg tumour, 2 osteoblastomas, 3 cases of Langerhans cell disease.*
[c]*Cementomas were interpreted from description to represent early periapical cemental dysplasia (see reference 1). Other = 1 fibro-osseous lesion, not otherwise specified, 1 monostotic fibrous dysplasia.*
[d]*Includes adenocarcinoma and metastatic lesions.*
[e]*Leukemia, 2 cases of multiple myeloma.*

showing significant findings. Preliminary data suggest that selective submission is a common practice.[16]

On a cautionary note, an unknown number of nonendodontic periapical lesions, initially diagnosed and treated as endodontic cases, would also be excluded from these survey studies, thus decreasing the percentage of significant periapical biopsies. Exclusion could occur in 2 ways. The first could occur when a periapical lesion in an endodontically treated case is belatedly submitted for examination after the lesion shows unexpected aggressive behaviour. These lesions would not be classified as endodontic cases and would be excluded from retrospective studies of periapical lesions. The second category of cases are those in which benign but expansile periradicular lesions, such as lateral periodontal or nasopalatine duct cysts, were misdiagnosed and the tooth treated endodontically. Subsequent surgery of the nonresolving periapical lesion would result in clinical success. However, the misdiagnosis and inappropriate treatment would not be identified.

Review of the Literature Describing Unusual Periapical Pathosis

There have been many reports documenting clinically confusing periapical lesions, although their incidence is unknown. Various developmental cysts, fibro-osseous lesions, infections, granulomatous inflammatory conditions and a wide range of benign or malignant neoplasms have been described. Additionally, radiographically confusing anatomic superimpositions have been discussed. **Table 1** shows the numbers and types of lesions that have been described. These are reviewed in the following sections.

Cysts

Cysts that mimic endodontically mediated periapical lesions include odontogenic keratocysts,[9,17–20] nasopalatine duct cysts,[21,22] contiguous residual cysts[23] and lateral periodontal cysts.[6] Within this group, the odontogenic keratocyst (OKC) is the most important because of its propensity for recurrence and aggressive behaviour. About 0.7% of putative radicular (periapical) cysts represent OKCs.[19] In one large OKC study,[17] 11.2% of the OKCs were identified *de novo* in the site of previously extracted teeth. Although it is possible that the teeth in these cases were removed for reasons unrelated to the contiguous radiolucency, this finding suggests the possibility that a periapical OKC prompted the tooth removal.

Other cyst types are not as aggressive. However, if root canal treatment is done in these cases, the cysts would continue to enlarge, independent of the success of the endodontic treatment. Further periapical surgery of the nonendodontic lesion would result in resolution.

Infections

Although actinomycosis is the most commonly documented infection,[24–34] histoplasmosis[35] and aspergillosis[6,36]

have also been described. These case reports typically describe the infections as a complication of endodontic treatment and not as a primary pathosis in the periapical area. However, identification of this complication is necessary to initiate appropriate follow-up antibiotic therapy.

Benign Aggressive Lesions

The most documented locally destructive lesion that has been mistaken for periapical disease is the central giant-cell granuloma.[6,9,37–40] This benign lesion of unknown origin was once thought to represent a reparative process. These lesions demonstrate a range of aggressive behaviour that is difficult to predict. In at least one case,[37] the associated tooth did not respond to electric pulp testing, but the pulp subsequently appeared vital after an opening was made to access the pulp. This suggests that vitality testing can be unreliable when lesions encroach on the root apex.

Other reported lesions have been central ossifying fibroma,[4] Pindborg tumour,[6] Langerhans cell disease,[10,43] osteoblastoma[10,41] and the central odontogenic fibroma.[42] Generally, delayed identification of these lesions would result in more extensive bone destruction and greater morbidity, but would not normally be expected to be life-threatening.

Benign Fibro-osseous Lesions

A specific type of fibro-osseous lesion called "periapical cemental dysplasia," which develops around root apices, represents a well-recognized diagnostic challenge. Diagnosis is particularly difficult for early lesions that do not show mineralization on radiographs. A multifocal presentation is helpful for discerning their nonendodontic nature, although focal presentations occur.[45,62] Careful clinical assessment, including taking a history of the affected area, radiographs and vitality testing, should usually establish the diagnosis. Radiographic features are more definitive in the later mineralizing stages. Typically treatment is not indicated in these cases.

Granulomatous Inflammation

Granulomatous inflammation[46–48] has been specifically described and distinguished from the granulation tissue found in periapical granulomas. Granulomatous inflammation can be elicited by a variety of agents, such as foreign materials, cholesterol derived from cell necrosis, or fungal and mycobacterial infections. However, this type of inflammation is relatively common in periapical biopsy material and might not result in a separate classification of the lesions showing this feature. The role of granulomatous inflammation in endodontic failure does not seem to be well understood but, in theory, could be important. At least one report[47] indicated that foreign body–induced granulomatous inflammation in periapical tissues resulted in a lesion that was refractory to endodontic therapy.

Malignant Lesions

Misdiagnosed malignant neoplasms cause the greatest concern and represent about 12% of documented cases. Presumably these cases are relatively rare and the documentation is disproportionate because of the significance of the missed diagnosis. A wide range of primary or metastatic malignant lesions have been reported, including osteosarcoma, lymphoma, plasma-cell tumours and leukemia; however, the most commonly reported malignancies are various forms of carcinoma.[10,11,43,44,49–61] Atypical features, summarized by Hutchison and others,[10] that suggest the possibility of neoplastic involvement include minimal caries, root resorption, irregular radiolucency, localized tooth mobility, anesthesia and failure of the periapical lesion to resolve after root canal treatment. Tooth vitality is also an important finding, but this determination may be difficult if the lesion encroaches on the apex.

Anatomic Superimpositions

Anatomic superimpositions are an obvious concern, but should not present a diagnostic problem. The most common presentation is the superimposition of the mental foramen. An unusual case involving a median mandibular salivary gland inclusion[63] has been described as a confounding radiographic presentation that suggests periapical disease.

Conclusions

A wide range of nonendodontic pathoses presenting in the periradicular region has been documented. The clinical implications vary depending on the lesion. The frequency with which this occurs is not known, but clinical sensitivity to these possibilities is important to minimize the possibility of misdiagnosis. It is useful to remember that vitality tests are not always reliable, necrotic and vital tissues can co-exist in the same tooth, and a nonvital tooth is not necessarily the reason for a periapical lesion.[64] Finally, the extent to which a nonendodontic lesion encroaching on the apex of a tooth can influence vitality testing has not been clarified. ➧

Dr. Peters *is professor, department of dentistry, faculty of medicine and dentistry, University of Alberta, Edmonton, Alberta.*

Dr. Lau *is a dentist in private practice in Edmonton, Alberta.*

Correspondence to: *Dr. Edmund Peters, 5085 Dentistry Pharmacy Centre, University of Alberta, Edmonton. AB T6G 2N8. E-mail: peters@ualberta.ca.*

The authors have no declared financial interests.

References

1. Bhaskar SN. Oral surgery - oral pathology conference No. 17, Walter Reed Army Medical Center. Periapical lesions — types, incidence, and clinical features. *Oral Surg Oral Med Oral Pathol* 1966; 21(5):657–71.

2. Seltzer S, Bender IB, Smith J, Freedman I, Nazimov H. Endodontic failures — an analysis based on clinical, roentgenographic and histologic findings. Part I. *Oral Surg Oral Med Oral Pathol* 1967; 23(4):500–16.

3. Stockdale CR, Chandler NP. The nature of the periapical lesion — a review of 1108 cases. *J Dent* 1988; 16(3):123–9.

4. Spatafore CM, Griffin JA Jr, Keyes GG, Wearden S, Skidmore AE. Periapical biopsy report: an analysis over a 10-year period. *J Endod* 1990; 16(5):239–41.

5. Nobuhara WK, del Rio CE. Incidence of periradicular pathoses in endodontic treatment failures. *J Endod* 1993; 19(6):315–8.

6. Kuc I, Peters E, Pan J. Comparison of clinical and histologic diagnoses in periapical lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 89(3):333–7.

7. Hakala PE, Calonius PE, Koskinen KP. Histologic evaluation of periapical areas of endodontically treated teeth with unsuccessful healing. *Proc Finn Dent Soc* 1980; 76(5-6):253–61.

8. Ramachandran Nair PN, Pajarola G, Schroeder HE. Types and incidence of human periapical lesions obtained with extracted teeth. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; 81(1):93–102.

9. Dahl EC. Diagnosing inflammatory and non-inflammatory periapical disease. *J Indiana Dent Assoc* 1991; 70(6):22–6.

10. Hutchison IL, Hopper C, Coonar HS. Neoplasia masquerading as periapical infection. *Br Dent J* 1990; 168(7):288–94.

11. Schlagel E, Seltzer RJ, Newman JI. Apicoectomy as an adjunct to diagnosis. *NY State Dent J* 1973; 29(3):156–8.

12. Weisman MI. The importance of biopsy in endodontics. *Oral Surg Oral Med Oral Pathol* 1975; 40(1):153–4.

13. Corcoran JF. The importance of periapical biopsy as a diagnostic tool in endodontics. *J Mich Dent Assoc* 1978; 60(10):523–6.

14. American Association of Endodontists. Appropriateness of care and quality assurance guidelines. 3rd ed. 1998.

15. Walton RE. Routine histopathologic examination of endodontic periradicular surgical specimens — is it warranted? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86(5):505.

16. Kuc I, Pan J, Peters E. Use of histopathologic exam for periapical lesions by general dentists and specialists. Abstract, American Academy of Oral and Maxillofacial Pathology meeting. May 1998, Dallas, Texas.

17. Brannon RB. The odontogenic keratocyst. A clinicopathologic study of 312 cases. Part I. Clinical features. *Oral Surg Oral Med Oral Pathol* 1976; 42(1):54–72.

18. Wright BA, Wysocki GP, Larder TC. Odontogenic keratocysts presenting as periapical disease. *Oral Surg Oral Med Oral Pathol* 1983; 56(4):425–9.

19. Stajcic Z, Paljm A. Keratinization of radicular cyst epithelial lining or occurrence of odontogenic keratocyst in the periapical region? *Int J Oral Maxillofac Surg* 1987; 16(5):593–5.

20. Nohl FS, Gulabivala K. Odontogenic keratocyst as periradicular radiolucency in the anterior mandible: two case reports. *Oral Surg Oral Med Oral Pathol* 1996; 81(1):103–9.

21. Terry BR, Bolanos OR. A diagnostic case involving an incisive canal cyst. *J Endod* 1989; 15(11):559–62.

22. Gulabivala K, Briggs PF. Diagnostic dilemma: an unusual presentation of an infected nasopalatine duct cyst. *Int Endod J* 1992; 25(2):107–11.

23. Weine FS, Silverglade LB. Residual cysts masquerading as periapical lesions: three case reports. *J Am Dent Assoc* 1983; 106(6):833–5.

24. Kalnins V. Actinomycotic granuloma. *Oral Surg Oral Med Oral Pathol* 1971; 32(2):276–7.

25. Hamner JE, Schaefer ME. Anterior maxillary actinomycosis: report of case. *J Oral Surg* 1965; 23:60–3.

26. Martinelli C, Rulli MA. Periapical cyst associated with actinomycosis. *Oral Surg Oral Med Oral Pathol* 1967; 24(6):817–20.

27. Kapsimalis P, Garrington GE. Actinomycosis of the periapical tissues. *Oral Surg Oral Med Oral Pathol* 1968; 26(3):374–80.

28. August DS, Levy BA. Periapical actinomycosis. *Oral Surg Oral Med Oral Pathol* 1973; 36(4):585–8.

29. Samanta A, Malik CP, Aikat BK. Periapical actinomycosis. *Oral Surg Oral Med Oral Pathol* 1975; 39(3):458–62.

30. Oppenheimer S, Miller GS, Knopf K, Blechman H. Periapical actinomycosis. *Oral Surg Oral Med Oral Pathol* 1978; 46(1):101–6.

31. Fergus HS, Savord EG. Actinomycosis involving a periapical cyst in the anterior maxilla. Report of a case. *Oral Surg Oral Med Oral Pathol* 1980; 49(5):390–3.

32. Weir JC, Buck WH. Periapical actinomycosis. Report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol* 1982; 54(3):336–40.

33. Craig RM, Andrews JD, Wescott WB. Draining fistulas associated with an endodontically treated tooth. *J Am Dent Assoc* 1984; 108(5):851–2.

34. Sakellariou PL. Periapical actinomycosis: report of a case and review of the literature. *Endod Dent Tramatol* 1996; 12(3):151–4.

35. Pisanty S. Histoplasmosis as periapical pathology: a case report. *J Oral Med* 1979; 34(4):116–8.

36. Khongkhunthian P, Reichart PA. Aspergillosis of the maxillary sinus as a complication of overfilling root canal material into the sinus: report of two cases. *J Endod* 2001; 27(7):476–8.

37. Sykaras SN. Central giant cell granuloma: report of a case. *Int Endod J* 1981; 14(3):185–7.

38. Martin LR. Systematic approach to endodontic diagnosis – a must! A case report. *Clin Prev Dent* 1982; 4(5):25–7.

39. Glickman GN. Central giant cell granuloma associated with a nonvital tooth: a case report. *Int Endod J* 1988; 21(3):224–30.

40. Dahlkemper P, Wolcott JF, Pringle GA, Hicks ML. Periapical giant cell granuloma: a potential endodontic misdiagnosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 90(6):739–45.

41. Ribera MJ. Osteoblastoma in the anterior maxilla mimicking periapical pathosis of odontogenic origin. *J Endod* 1996; 22(3):142–6.

42. Huey MW, Bramwell JD, Hutter JW, Kratochvil FJ. Central odontogenic fibroma mimicking a lesion of endodonti*c* origin. *J Endod* 1995; 21(12):625–7.

43. Blevins C, Dahlin DC, Lovestedt SA, Kennedy RLJ. Oral and dental manifestations of histiocytosis X. *Oral Surg Oral Med Oral Pathol* 1959; 12:473–83.

44. Wannsfors K, Hammarstrom L. Periapical lesions of mandibular bone: difficulties in early diagnostics. *Oral Surg Oral Med Oral Pathol* 1990; 70(4):483–9.

45. Wilcox LR, Walton RE. Case of mistaken identity: periapical cemental dysplasia in an endodontically treated tooth. *Endod Dent Traumatol* 1989; 5(6):298–301.

46. Koppang HS, Koppang R, Solheim T, Aarnes H, Stolen SO. Cellulose fibers from endodontic paper points as an etiological factor in postendodontic periapical granulomas and cysts. *J Endod* 1989; 15(8):369–72.

47. Nair PN, Sjogren U, Krey G, Sundqvist G. Therapy-resistant foreign body giant cell granuloma at the periapex of a root-filled human tooth. *J Endod* 1990; 16(12):589–95.

48. Talacko AA, Radden BG. Oral pulse granuloma: clinical and histopathological features. A review of 62 cases. *Int J Oral Maxillofac Surg* 1988; 17(6):343–6.

49. Burkes EJ Jr. Adenoid cystic carcinoma of the mandible masquerading as periapical inflammation. *J Endod* 1975; 1(2):76–8.

50. Milobsky SA, Milobsky L, Epstein LI. Metastatic renal adenocarcinoma presenting as periapical pathosis in the maxilla. *Oral Surg Oral Med Oral Pathol* 1975; 39(1):30–3.

51. Block RM, Mark HI, Bushell A. Metastatic carcinoma of the breast mimicking periapical disease in the mandible. *J Endod* 1977; 3(5):197–9.

52. Coonar HS. Primary intraosseous carcinoma of maxilla. *Br Dent J* 1979; 147(2):47–8.

53. Copeland RR. Carcinoma of the antrum mimicking periapical pathology of pulpal origin: a case report. *J Endod* 1980; 6(7):655–6.

54. Spott RJ. Metastatic breast carcinoma disguised as periapical disease in the maxilla. *Oral Surg Oral Med Oral Pathol* 1985; 60(3):327–8.

55. Nevins A, Ruden S, Pruden P, Kerpel S. Metastatic carcinoma of the mandible mimicking periapical lesion of endodontic origin. *Endod Dent Traumatol* 1988; 4(5):238–9.

56. Jee A, Domboski M, Milobsky SA. Malignant fibrohistiocytoma of the maxilla presenting with endodontically involved teeth. *Oral Surg Oral Med Oral Pathol* 1978; 45(3):464–9.

57. Spatafore CM, Keyes G, Skidmore AE. Lymphoma: an unusual oral presentation. *J Endod* 1989; 15(9):438–41.

58. Mopsik ER, Milobsky SA. Malignant lymphoma presenting as periapical pathology: a report of two cases. *MSDA J* 1995; 38(4):175–9.

59. Hicks MJ, Flaitz CM. External root resorption of a primary molar: "incidental" histopathologic finding of clinical significance. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 92(1):4–8.

60. Peterson DE, Gerad H, Williams LT. An unusual instance of leukemic infiltrate. Diagnosis and management of periapical tooth involvement. *Cancer* 1983; 51(9):1716–9.

61. Shah N, Sarkar C. Plasmacytoma of anterior maxilla mimicking periapical cyst. *Endod Dent Traumatol* 1992; 8(1):39–41.

62. White SC, Pharoah M, editors. Oral radiology. Principles and interpretation. 4th ed. St. Louis: Mosby Inc.; 2000. p. 450–4.

63. Childers EL, Johnson JD, Warnock GR, Kratochvil FJ. Asymptomatic periapical radiolucent lesion found in an area of previous trauma. *J Am Dent Assoc* 1990; 121(6):759–60.

64. Chambers IG. The role and methods of pulp testing in oral diagnosis: a review. *Int Endod J* 1982; 15(1):1–15.