REVIEW ARTICLE

Leukemia and Lymphoma Mimicking Periapical Conditions Resulting in Endodontic Treatment: A Systematic Review

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SIGNIFICANCE

Leukemia and lymphoma can mimic periapical conditions, creating diagnostic challenges and often leading to inappropriate endodontic treatments. Such misdiagnoses delay proper care and jeopardize patient outcomes. This review provides guidance to endodontists on distinguishing hematolymphoid neoplasms from periapical conditions to enhance clinical practice.

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ABSTRACT

Introduction: Leukemia and lymphoma mimicking periapical conditions can lead to significant diagnostic pitfalls. Guidance for endodontists in managing such cases is barely explored. This systematic review aimed to summarize the clinicopathologic, imaging, and management aspects of leukemia/lymphoma that mimicked periapical conditions and resulted in endodontic treatment. **Methods:** Searches were conducted in PubMed, Embase, Scopus, Web of Science, and LILACS, supplemented by manual scrutiny and gray literature. Case reports and/or case series were included. Critical appraisal of the studies was performed using the Joanna Briggs Institute tool. **Results:** Among 3,617 identified records, 32 studies involving 37 individuals (mean age 43.6 years; male-to-female ratio 1.2:1) were included. Diffuse large B-cell lymphoma was diagnosed in 21 (56.8%) individuals. The anterior maxilla and posterior mandible were the most frequently affected sites (29.7% each). Radiographically, 97.3% of the lesions exhibited radiolucency in the periapical region. Endodontic treatment preceded the diagnosis of leukemia/lymphoma in 94.6% of cases, while retreatment occurred in 5.4%. The mean time to final diagnosis was 4.9 months. **Conclusion:** Leukemia and lymphoma can be misdiagnosed as periapical conditions, leading to inappropriate endodontic treatments and delayed diagnoses. Endodontists should become familiar with the broad clinicoradiographic spectrum of these rare, but potentially life-threatening hematolymphoid malignancies. *(J Endod 2025;51:106–117.)*

KEY WORDS

Dental pulp diseases; diagnostic errors; differential diagnoses; jaws; leukemia; lymphoma; periapical diseases

Leukemias and lymphomas are hematolymphoid malignancies that affect the cells of the hematopoietic and lymphatic systems[1-3]. In 2022, leukemias were ranked as the 13th most prevalent cancer worldwide, while the incidence of lymphomas ranged from 82,409 to 553,010 new cases[4]. Leukemia is characterized by the abnormal proliferation of immature blood cells in the bone marrow, which subsequently enter the bloodstream. It can present as either acute or chronic[2,3,5,6]. Lymphomas are tumors originating from B, T, or NK lymphocytes and are classified into non-Hodgkin lymphomas and Hodgkin lymphomas (HL). These lesions can vary in behavior from indolent to highly aggressive[1,7,8].

Approximately 29%–48% of malignant lesions arising from hematopoietic and lymphoid tissues affect the stomatognathic system[9]. The clinicopathologic diversity of oral and oropharyngeal leukemias/lymphomas presents a significant diagnostic challenge, further complicated by the absence of distinctive radiographic features[9-13]. Systematic reviews have shown that the overlap between nonendodontic and endodontic lesions (ie, periapical conditions) often leads to difficulties in diagnostic differentiation, potentially resulting in incorrect diagnoses and inappropriate treatments[14-16]. Thus, endodontists may

face challenges when treating individuals with rare conditions and might not be fully aware of the specific oral health needs or key features of hematolymphoid malignancies[15,17].

Current knowledge provides limited guidance on the early recognition and management of nonendodontic lesions, particularly leukemias and lymphomas, which can resemble periapical conditions[14,15]. This gap in the literature provides an opportunity to evaluate the management of these hematolymphoid malignancies in the context of the differential diagnosis of pulpal/apical conditions according to the classification proposed by the American Association of Endodontists[18]. Therefore, the aim of the present systematic review was to summarize information on the clinicopathologic and imaging characteristics, as well as the management aspects of leukemia and lymphoma that mimicked periapical conditions and resulted in endodontic treatment.

MATERIALS AND METHODS

Eligibility Criteria

The eligibility criteria were case reports and case series that provided clinical, radiographic, and histopathologic data of leukemia/lymphoma mimicking conditions that had been treated endodontically. The 5th edition of the World Health Organization classification of hematolymphoid tumors was used to categorize leukemia/lymphoma[1]. Exclusion criteria were laboratory studies, reviews, letters, book chapters, conference abstracts, animal studies, incomplete articles, studies with insufficient data on diagnosis and treatment, and borderline diseases. The study design followed the PECO framework: P (Population): individuals; E (Exposure): leukemia/lymphoma mimicking periapical conditions that had been misdiagnosed and treated endodontically; C (Comparison): not applicable; O (Outcome): clinicopathologic and imaging characteristics.

Databases and Search Strategies

Electronic searches were performed in March 2023 across the following databases: PubMed (National Library of Medicine), Embase (Elsevier), Scopus (Elsevier), Web of Science (Clarivate Analytics), and LILACS (Latin America and the Caribbean Literature on Health Sciences). The searches included indexed articles without restrictions on language, publication date, or geographic region. An update was performed in October 2024. The search strategies used Boolean operators to link terms and keywords, as follows: (lymphoma OR leukemia OR leukaemia) AND (mandible OR maxilla OR jaw OR gnathic OR gnathic bones OR periapical). Hand searches involved cross-checking the reference lists of included articles, and gray literature was assessed using Google Scholar, with the search limited to the first 200 records[19]. Duplicate references across databases were removed using the Rayyan platform (http://rayyan.qcri.org).

Study Selection

Study selection was performed independently by 2 authors (I.S.M.Q. and J.A.A.A.) in 2 stages. In the first stage, each author reviewed the titles and abstracts of studies to identify those that appeared potentially relevant and met the inclusion criteria. In the second stage, the authors assessed the full texts and excluded studies that did not meet the eligibility criteria. Any discrepancies between authors were resolved through discussion with a third author (G.C.S.) until a consensus was reached.

Data Coding and Extraction

The following data were extracted: author(s) name(s), year of publication, country, age and sex of individuals, clinical presentation, symptomatology, duration of symptoms, anatomical location, radiographic findings, histopathologic findings, immunohistochemical markers, molecular/genetic information (when available), comorbidities, treatment provided, and outcomes. Data collection was performed by one author (I.S.M.Q.) and was double-checked by a second author (J.A.A.A.).

Critical Appraisal

The case reports and case series were appraised by 2 authors (I.S.M.Q. and J.A.A.A.) using the Joanna Briggs Institute tools[20,21]. The case reports were appraised for the clarity of the patient's demographic characteristics, medical history, current clinical condition, diagnostic approach, treatment, postintervention status, adverse events, and lessons learned. The case series were appraised for the clarity of inclusion criteria, the method of identifying the condition, completeness of participant inclusion, demographic characteristics, current clinical status, outcomes, epidemiologic data, and the quality of statistical analysis. Each criterion was rated as "yes," "no," "unclear," or "not applicable." Any discrepancies were resolved by a third author (G.C.S.).

Data Analysis

Data were tabulated in Microsoft Excel 2019 (Microsoft, Redmond, WA, USA) and analyzed descriptively using GraphPad Prism 8.0.0 for Windows (GraphPad Software, San Diego, CA, USA).

Protocol and Registration

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[22]. The review protocol was registered with the International Prospective Register of Systematic Reviews under registration number CRD42024530631.

RESULTS

Literature Search and Geographic Distribution

The electronic search yielded 3,617 articles. After removing 2,148 duplicates, 1,469 references were assessed for eligibility, resulting in the inclusion of 20 articles. Additionally, 12 articles meeting the eligibility criteria were identified through manual searches and gray literature. Thus, a total of 32 articles comprising 37 individuals were analyzed. These included 26 case reports[23-49] and 6 case series[50-55]. Figure 1 depicts the flowchart outlining the article selection process.

The studies were published between 1989[46] and 2024[55] and were from the United States[25-28,30,32,37,41,43,48,50,51,55], Canada[54], Italy[23,29,44,45], the Netherlands[52], Sweden[53], Greece[47], Japan[36,40,46], India[31,38], China[49], Israel[24], Jordan[33], Brazil[34,39,42], and Australia[35].

Clinicodemographic Aspects

Nineteen (51.4%) individuals were male and 16 (43.2%) were female, resulting in a male-to-female ratio of 1.2:1. The mean age of the individuals was 43.6 (±18.2) years (range: 4–77 years). Data on sex were unavailable in 2 (5.4%) studies. The medical history of the individuals primarily revealed that 6 (14.3%) had cancer. Pain was reported in 16 (16.8%) individuals, followed by paresthesia (n = 9; 9.5%) and tenderness (n = 8; 8.4%). Intraorally, edema was the most common clinical feature (n = 34; 35.8%). The anterior maxilla and posterior mandible were the most frequently affected sites (n = 11; 29.7% each),

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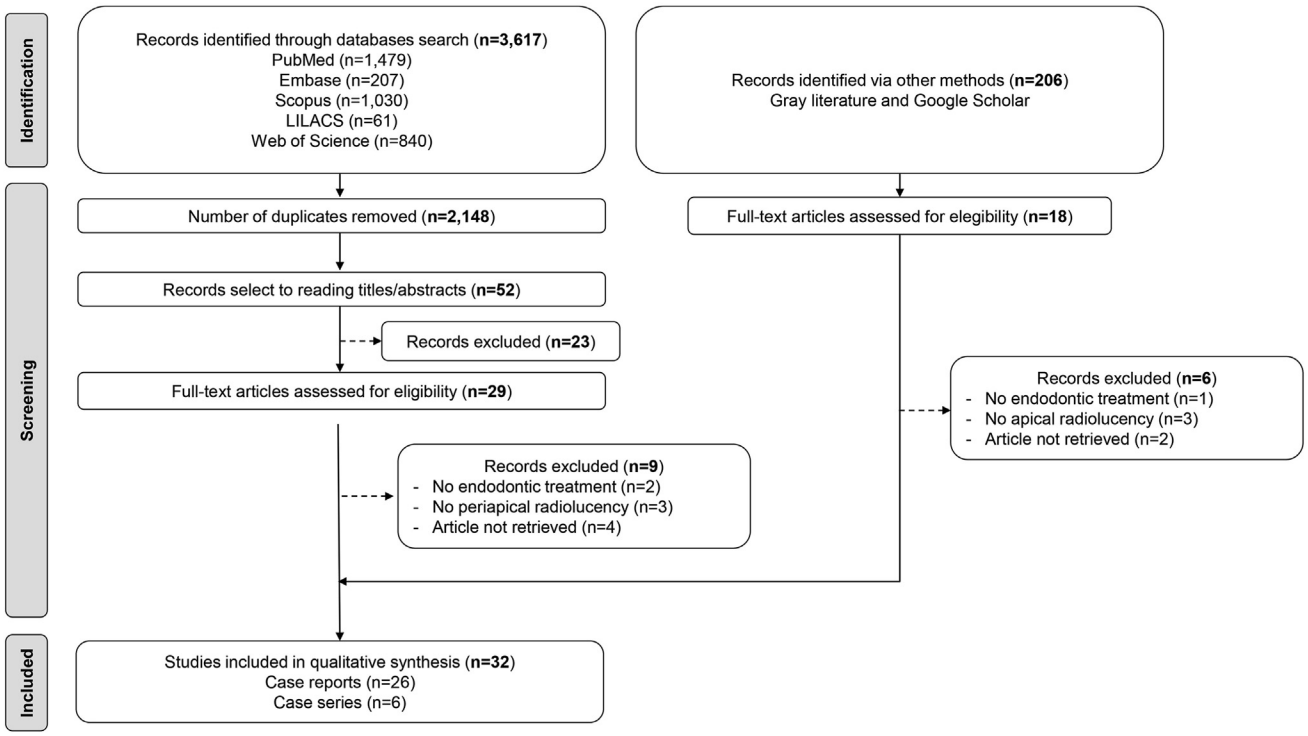

FIGURE 1 – Flowchart depicting article selection process.

although some cases involved multiple locations concurrently (Table 1).

Endodontic Considerations

Tooth mobility (n = 11; 30.5%), positive percussion (n = 9; 25.0%), and pulp vitality (n = 9; 25.0%) were the most frequently reported endodontic and periodontal findings. Radiographically, the periapical region was most commonly affected (n = 36; 97.3%). Radiolucent lesions were found in 36 (97.3%) individuals, with 10 (27.0%) of these showing diffuse borders. Poorly defined borders and enlarged borders were identified in 6 (16.2%) cases each. Periodontal ligament enlargement was present in 7 (18.9%) cases. Cortical perforation and loss of lamina dura were each found in 6 (16.2%) cases, and sinus involvement was noted in 5 (13.5%) cases.

Periodontal/periradicular condition was the primary diagnostic hypothesis (n = 12; 18.7%). Endodontic treatment was administered to 35 (94.6%) individuals, while 2 (5.4%) underwent retreatment. Concurrent antibiotic therapy was provided to 16 (42.2%) individuals, and tooth extractions were performed in 10 (26.4%) patients.

To better illustrate periapical involvement, we present clinicoradiographic, histopathologic, and immunohistochemical images of 2 unpublished cases of lymphomas that initially mimicked periapical conditions and were subsequently treated endodontically (Figs. 2 and 3).

Diagnostic Workup for Leukemia/Lymphoma, Treatment, and Outcomes

Biopsies were performed on all 37 (100%) individuals. Immunohistochemistry was used in 23 (62.2%) cases, with the panel including markers for T-, B-, and NK-cells, mesenchymal and muscle cells, cell proliferation, epithelial and hematopoietic stem cells, among others. Non-Hodgkin lymphomas was the most common diagnosis (n = 34; 91.9%), with diffuse large B-cell lymphoma being the predominant subtype (n = 21; 56.8%). HL was found in one (2.7%) case. Leukemias were diagnosed in 2 (5.4%) individuals, including chronic lymphocytic leukemia (n = 1; 2.7%) and acute lymphocytic leukemia (n = 1; 2.7%). The mean time to final diagnosis was 4.9 months (range: 0.5–36 months). Supplementary File 1 summarizes data on antineoplastic therapy, outcomes, and other variables.

Critical Appraisal

Most case reports clearly described the demographic characteristics and current clinical condition of the individuals. The patients' histories and diagnostic methods were well detailed in all cases. However, treatment details were unclear in 7.7% of the reports and not provided in 11.5% of the articles. The postintervention status was not described in 19.2% of the articles. Adverse events were not reported in one study and were unclear in another. Two articles did not clearly convey important lessons (Supplementary File 2). In the case series, the methods for identifying the condition, presentation of demographic data, and outcomes were well presented across all articles. The condition was consistently measured for most individuals in the majority of articles. However, the inclusion criteria for participants and statistical analysis were not well defined in 3 series. Clinical information for individuals was not clearly detailed in 2 studies. Only one case series provided complete information on participant inclusion (Supplementary File 3).

DISCUSSION

Leukemias and lymphomas of the jaws are rare, but can initially present as periapical conditions, complicating diagnosis and potentially delaying appropriate treatment. Approximately 5% of malignant neoplasms in the head and neck region are lymphomas[56], with 50% of these occurring in the oral and

TABLE 1 - Clinical, Demographic, and Pathologic Aspects, Radiographic Findings, Endodontic Treatment, Time of Evolution, and Outcomes of Leukemia/Lymphoma Cases Retrieved in the Literature

Study	Age	Sex	Anatomical location	Radiographic findings	Endodontic management	Leukemia/ lymphoma diagnosis	Time lapse between first signs and diagnosis	Outcome
Angiero et al[23]	56	F	Anterior mandible	Radiolucent lesion with disruption of the lamina dura and thickening of the periodontal ligament	Endodontic treatment and antibiotic therapy	DLBCL	~2 wks	DOD
Ardekian et al[24]	16	M	Posterior mandible	Radiolucent lesion with poorly defined borders and thickening of the periodontal ligament	Endodontic treatment	BL	2 wks	NI
Bavitz et al[25]	46	F	Anterior maxilla	Radiolucent lesion with diffuse borders	Endodontic treatment	NHL	Several wks	DFS
Biggs & Sabala[26,27]	77	F	Posterior mandible	Radiolucent lesion with diffuse borders and widespread loss of trabecular pattern	Endodontic treatment	NHL	2 mo	DOD
Bugshan et al[28]	54	M	Posterior mandible	Radiolucent lesion with poorly defined borders	Endodontic treatment	DLBCL	~1 mo	NI
Cabras et al[29]	15	F	Posterior mandible	Radiolucent lesion	Endodontic treatment and antibiotic therapy	BL	NI	DFS
Dolan et al[30]	68	M	Anterior maxilla and anterior and posterior mandible	Radiolucent lesion with cortical perforation and ground-glass opacity	Endodontic treatment	NHL	~4 mo	DFS
Eisenbud et al[50]	49	F	Anterior mandible	Radiolucent lesion with loss of alveolar attachment	Endodontic treatment	DLBCL	Several mo	DOC
	44	M	Posterior mandible	Radiolucent lesion	Endodontic treatment	DLBCL	NI	DFS
	42	M	Anterior maxilla	Radiolucent lesion	Endodontic treatment	DLBCL	NI	DOD
Faisal et al[31]	31	M	Posterior maxilla	Rarefaction of the alveoli and maxillary sinus walls	Endodontic treatment	NHL	~3 mo	DFS
Fischer et al[32]	34	M	Posterior maxilla	Radiolucent lesion with poorly defined borders	Endodontic treatment	DLBCL	~5 mo	NI
Hassona et al[33]	75	M	Posterior mandible	Radiolucent lesion with poorly defined borders and cortical perforation	Analgesic prescription and endodontic retreatment	DLBCL	5 wks	DOD
Hopp et al[34]	39	M	Anterior mandible	Radiolucent lesion with diffuse borders, thickening of the periodontal ligament, and disruption of the lamina dura	Endodontic treatment	DLBCL	2 yrs	DFS
Jessri et al[35]	32	M	Posterior mandible	Radiolucent lesion with diffuse borders, a “moth-eaten” appearance, and cortical bone narrowing	Endodontic treatment	DLBCL	~3 mo	DFS
Kawasaki et al[36]	60	F	Posterior mandible	Radiolucent lesion with cortical perforation	Endodontic treatment	NHL	~3 wks	DFS
Keyes et al[51]	24	M	Anterior maxilla	Radiolucent lesion	Endodontic treatment and antibiotic therapy	HL	~3 mo	DFS
	NI	NI	Posterior mandible	Radiolucent lesion with cotton wool radiopacity	Endodontic treatment and endodontic retreatment	CLL	29 mo	DFS

(*continued on next page*)

TABLE 1 - Continued

Study	Age	Sex	Anatomical location	Radiographic findings	Endodontic management	Leukemia/ lymphoma diagnosis	Time lapse between first signs and diagnosis	Outcome
Kluin et al[52]	52	F	Posterior maxilla	Radiolucent lesion	Endodontic treatment and antibiotic therapy	NHL	9 mo	DFS
Koivisto et al.[37]	56	F	Posterior maxilla	Radiolucent lesion with diffuse borders and disruption of the lamina dura	Endodontic treatment	DLBCL	~3 mo	DFS
Kumar et al[38]	41	F	Anterior maxilla and mandible	Radiolucent lesion with poorly defined borders	Endodontic treatment	DLBCL	~1 mo	DOD
Mendonça et a.[39]	38	F	Anterior maxilla	Radiolucent lesion with diffuse borders and cortical perforation	Endodontic treatment	DLBCL	~2 mo	DFS
Mitsudo et al[40]	16	M	Posterior maxilla and mandible	Radiolucent lesion with disruption of the lamina dura and loss of alveolar attachment	Endodontic treatment	BL	1 mo	DOD
Nosrat et al[41]	40	F	Anterior maxilla	Radiolucent lesion with loss of alveolar attachment and cortical perforation	Endodontic treatment	DLBCL	11 mo	DFS
Pereira et al[42]	48	M	Anterior mandible	Radiolucent lesion with diffuse borders, external resorption, and cortical perforation	Endodontic treatment	DLBCL	5 mo	DFS
Shilkofski et al[43]	72	M	Anterior maxilla	Radiolucent lesion with calcific metamorphosis and cortical perforation	Endodontic treatment and antibiotic therapy	DLBCL	~1 mo	UT
Sinjari et al[44]	38	M	Anterior mandible	Radiolucent lesion with thickening of the periodontal ligament and cortical perforation	Endodontic treatment	LBCL	NI	DFS
Sivolella et al[45]	52	M	Posterior mandible	Radiolucent lesion with irregular borders	Endodontic treatment	BL	6 wks	ROS
Sugihara et al[46]	4	NI	Posterior mandible	Radiolucent lesion with diffuse borders, thickening of the periodontal ligament, disruption of the lamina dura, and widespread loss of the trabecular pattern	Endodontic treatment and antibiotic therapy	ALL	~2 mo	DOD
Vaia-Aikaterini et al[47]	56	F	Anterior maxilla	Radiolucent lesion	Endodontic treatment and antibiotic therapy	DLBCL	NI	DFS
Wannfors & Hammarström[53]	45	F	Posterior mandible	Radiolucent lesion with diffuse borders, thickening of the periodontal ligament, and abnormality of trabecular pattern	Endodontic treatment	NHL	NI	DFS

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TABLE 1 - Continued

Study	Age	Sex	Anatomical location	Radiographic findings	Endodontic management	Leukemia/ lymphoma diagnosis	Time lapse between first signs and diagnosis	Outcome
Wong et al[54]	50	M	Anterior maxilla	Radiolucent lesion	Endodontic treatment	DLBCL	~6 mo	UT
	31	F	Anterior maxilla	Radiolucent lesion	Endodontic treatment	DLBCL	~5 mo	UT
Wongpattaraworakul et al[55]	61	M	Anterior maxilla	Radiolucent lesion with well-defined borders	Endodontic treatment	DLBCL	NI	ROS
	68	F	Posterior mandible	Radiolucent lesion with poorly defined borders	Endodontic treatment	DLBCL	~4 mo	DFS
Wright & Radman[48]	37	F	Anterior mandible	Radiolucent lesion with diffuse borders	Endodontic treatment	DLBCL	~4 mo	DFS
Yang et al[49]	6	M	Posterior maxilla and mandible	Radiolucent lesion with thickening of the periodontal ligament	Endodontic treatment	ALCL	~5 mo	DFS

ALCL, anaplastic large cell lymphoma; ALL, acute lymphocytic leukemia; BL, Burkitt lymphoma; CLL, chronic lymphocytic leukemia; DFS, disease free survival; DLBCL, diffuse large B-cell lymphoma; DOC, died of other cause; DOD, died of disease; F, female; HL, Hodgkin lymphoma; LBCL, large B-cell lymphoma; M, male; NHL, non-Hogkin lymphoma; NI, not informed; ROS, referred to oncology service; UT, undergoing treatment.

maxillofacial region[57]. A recent study of 781 individuals with lymphoma/leukemia found oral malignant infiltrations in 3.2% of cases, primarily affecting the gingiva and being most common among those with acute myeloid leukemia[13]. In the present review, diffuse large B-cell lymphoma was the most frequently diagnosed type of lymphoma, consistent with findings from previous multicenter studies[10,11]. Males were slightly more affected than females, and most cases occurred in the fourth and fifth decades of life. Nevertheless, current literature on lymphomas involving the oral and oropharyngeal regions shows a tendency for both sexes to be affected in the seventh decade of life, with lesions frequently located in the palate[10]. Clinically, these conditions may present with gingival enlargement, pain, bleeding, and tooth mobility[10,13].

It has been reported that 49% of lymphomas located in periapical regions were initially misdiagnosed as periapical pathoses, leading to inappropriate endodontic treatments[14]. Erroneous pulp-based diagnoses and subsequent endodontic treatments caused delays in the final diagnosis ranging from 2 weeks[24] to more than 2 years[51]. Initial diagnoses often included odontogenic periapical lesions, apical abscesses, and osteomyelitis, with malignant lesions considered only as a last hypothesis. In cases initially diagnosed as periapical lesions of pulp origin, individuals underwent endodontic treatment, which sometimes included antibiotic therapy, retrofilling, and endodontic reintervention[23-28,30-55]. Additional interventions also included tooth extraction, root resection, and subgingival scaling[24,27-29,36,41,45,46,50,51,54]. In cases where professionals opted for an incisional biopsy as the primary diagnostic approach following initial endodontic treatment[25,30-32,35,37-40,42-44,47,50,52,54,55], the decision may have been influenced by the perceived aggressiveness of a potential nonendodontic periapical lesion[58]. In routine cases of teeth presenting with signs and symptoms suggestive of endodontic conditions (eg, apical periodontitis)[59], professionals often choose endodontic treatment as the initial approach without considering the possibility of malignant neoplasms[15].

Radiographically, leukemias/lymphomas typically appear as nonspecific osteolytic lesions characterized by homogeneous radiolucency, irregular shapes, and diffuse margins. These lesions may be associated with the dental apex[9]. The presence of diffuse margins, which is uncommon in dental infections, can serve as a radiographic indicator of malignancy.

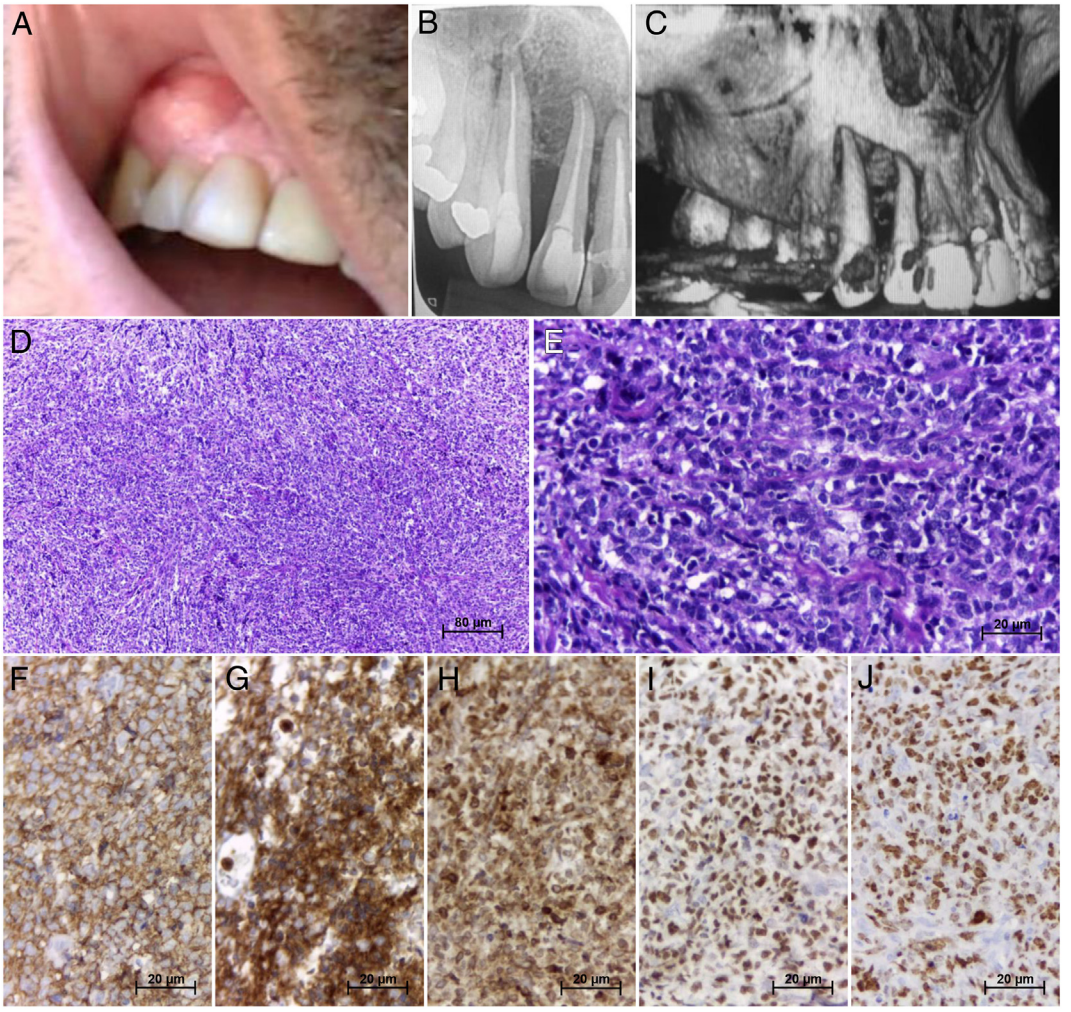

FIGURE 2 – Clinical, radiographic, histopathologic, and immunohistochemical features of a diffuse large B-cell lymphoma mimicking a periapical condition. (*A*) A 56-year-old man presented with a dome-shaped nodule in the maxillary gingival region between the right lateral incisor and canine. The nodule was firm, had an intact mucosal surface, and measured 2.0 × 1.0 cm. (*B*) Periapical radiography shows an osteolytic lesion with ill-defined borders, involving the apices of the right central and lateral incisors, canine, and first premolar. The right central and lateral incisors, as well as the canine, had previously undergone endodontic treatment with their canals filled with obturation materials. (*C*) Severe bone loss is observed in the three-dimensional reconstruction from cone-beam computed tomography. (*D*) At lower magnification, diffuse infiltration of lymphoid cells is evident, characterized by large neoplastic cells with a distinctive "starry sky" appearance. (*E*) The neoplastic cells consist of centroblasts with large, noncleaved nuclei, displaying round, vesicular nuclei with prominent nucleoli. The neoplastic cells express (*F*) CD20, (*G*) CD10, (*H*) BCL2, and (*I*) BCL6. (*J*) The Ki-67 index is high (hematoxylin and eosin staining, original magnification × 100 and × 400; immunohistochemistry staining, original magnification × 400).

However, chronic apical abscesses can also exhibit diffuse radiographic characteristics and cortical bone disruptions[60]. The periapical radiograph, commonly used as an adjunctive tool in endodontic treatment, was identified in most of the reviewed cases, with radiolucency being the predominant finding. Additionally, cases where leukemia/lymphoma mimicked endodontic conditions showed cortical bone disruption, changes in trabecular patterns, thickening of the periodontal ligament, alteration of the lamina dura, sinus involvement, and loss of alveolar support.

According to the diagnostic nomenclature recommended by the American Association of Endodontists, there are 13 pulpal and periapical conditions[18,61]. As noted earlier, the periapical region can be affected by a variety of diseases, including lymphomas and leukemias, regardless of pulp vitality or even in teeth that have been previously endodontically treated. This can lead to conditions that mimic endodontic conditions[15,16,58,59]. In such instances, misdiagnosis can result in inappropriate or unnecessary treatments, potentially worsening the underlying disease and leading to adverse outcomes, including the risk of the patient's death due to delays in receiving the correct treatment[15].

For healthy teeth with vital pulp that respond positively to thermal and/or electrical tests, and where periapical radiographs reveal radiolucency, treatment should not be initiated until it is confirmed that the condition is of endodontic origin[62]. In cases of uncertainty, more precise diagnostic tests should be performed, and treatment should be deferred until a definitive diagnosis is obtained. Teeth with healthy pulp may also show radiographic findings suggestive of malignant neoplasms, which require nonendodontic intervention[58,63]. For necrotic, asymptomatic pulp with evident radiolucency, endodontic treatment should be pursued, as this indicates an endodontic infection[62,64-66]. If the lesion does not regress and instead enlarges, malignancy should be suspected. In such cases, however, the

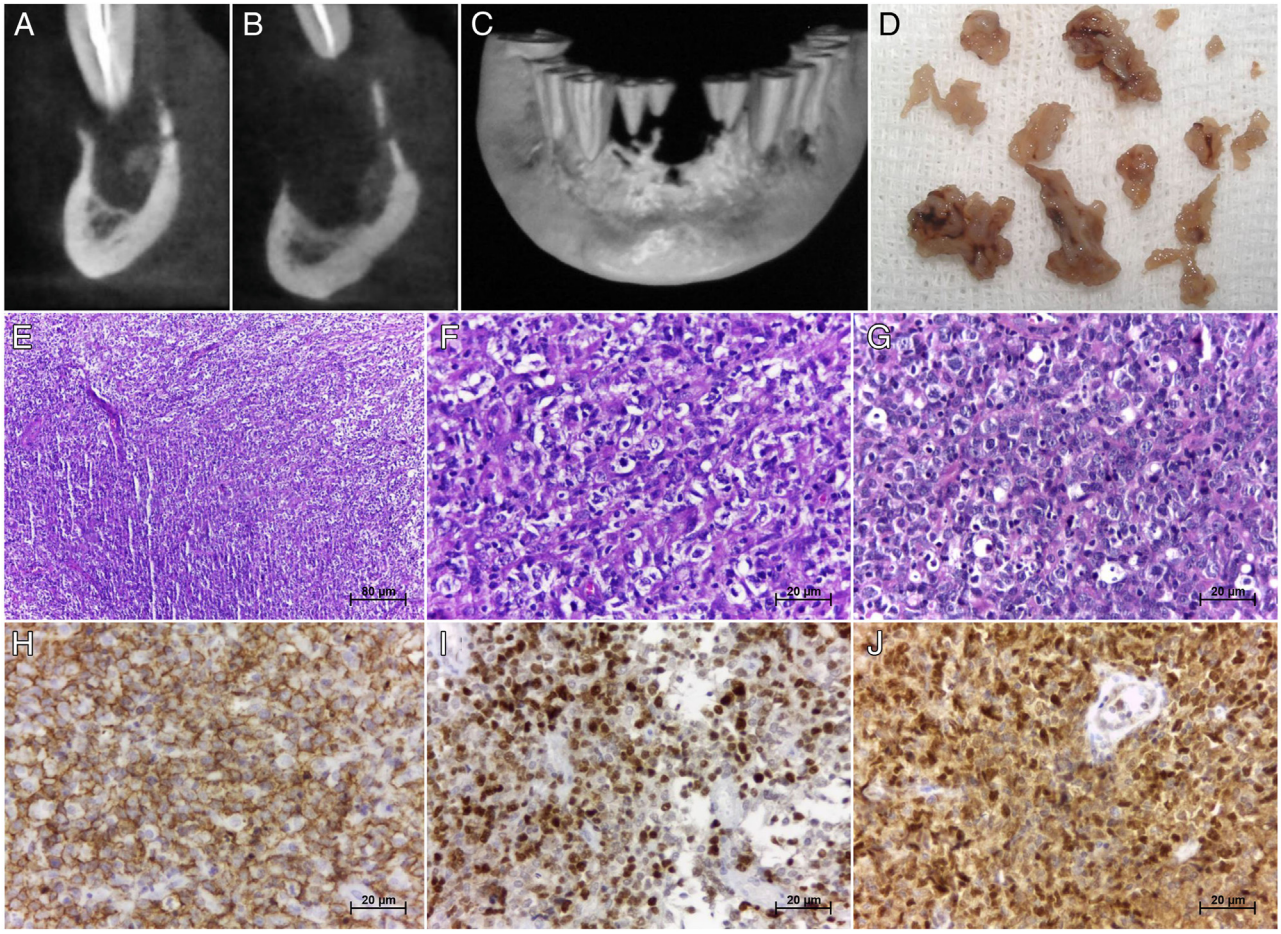

FIGURE 3 – Radiographic, macroscopic, histopathologic, and immunohistochemical features of a diffuse large B-cell lymphoma mimicking a periapical condition. (*A-C*) A 33-year-old man presented with an osteolytic lesion affecting the apices from the mandibular right first premolar to the left canine, evolving over 1 month. The lesion has ill-defined borders, with root resorption, tooth displacement, and cortical disruption, the largest diameter measuring approximately 40 mm. The right canine had been previously undergone endodontic treatment, with the canal obturated with filling material. (*D*) Gross appearance shows multiple fragments of soft tissue with irregular and smooth surfaces of fibrous consistency, predominantly brownish in color. (*E*) Low-power view reveals a diffuse lymphoid infiltrate of large neoplastic cells with a "starry sky" appearance. (*F-G*) Neoplastic cells include centroblasts with large, noncleaved nuclei featuring round, vesicular nuclei with multiple small nucleoli, and immunoblasts with oval and round vesicular nuclei and a prominent nucleolus. Atypical mitotic figures are also observed. The neoplastic cells express (*H*) CD20, (*I*) MUM1, and (*J*) BCL6 (hematoxylin and eosin staining, original magnification × 100 and × 400; immunohistochemistry staining, original magnification × 400).

patient should be promptly referred to an oral surgeon for further investigation. This is crucial because, as highlighted by Howell et al[67], the complexity of lymphoma often leads to diagnostic delays despite significant efforts by both patients and healthcare professionals to expedite the process. Even if lymphoma/leukemia is confirmed, endodontic treatment may still be necessary if there is a prior or concurrent endodontic condition alongside the more serious disease.

For previously endodontically treated teeth presenting with pain, with or without swelling, and radiographic evidence of treatment failure and persistent periapical radiolucency, reintervention is recommended[62,68], even if there is a suspicion of a concomitant malignant neoplasm[58]. Persistent pain and infection in these cases require endodontic intervention[64-66]. The literature documents that nonendodontic periapical lesions, including salivary gland neoplasms, odontogenic cysts and tumors, benign bone tumors, and infectious diseases, occur at an approximate rate of 4.2%[16]. Such conditions may present with bone pathology adjacent to teeth with normal or nonvital pulp. A systematic review has shown that the occurrence of nonendodontic malignant periapical lesions is similar in both sexes, with the majority of diagnoses made in the fifth decade of life. Among these, metastases were the most frequent diagnosis, accounting for nearly 27% of cases[15].

Of clinical relevance, the present review emphasizes that to avoid misdiagnoses and potential legal consequences of negligence, clinicians and endodontists must have a thorough understanding of oral and maxillofacial anatomy, differential diagnosis, and the prevalence of relevant diseases[69]. Accurate diagnosis relies on a detailed patient history, meticulous physical examination, and reliable diagnostic tools, such as pulpal sensitivity tests, and imaging studies[63]. Systematic follow-up after endodontic treatment is essential, as endodontic lesions typically regress with appropriate therapy[70]. Policy guidelines should prioritize the inclusion of hematolymphoid malignancies in the differential diagnosis of persistent or atypical periapical lesions. In such cases, a biopsy should be performed, and the sample should always be submitted to anatomopathologic examination to ensure diagnostic accuracy. It is recommended that endodontists or clinicians, who are managing the patient,

provide relevant clinical information (eg, history of hematologic disorders, known predisposing conditions or syndromes, previous malignancies, and exposure to antineoplastic therapies) and ensure that imaging findings are accessible to the oral surgeon and/or oral pathologist[71]. It is important to note that in the reviewed cases, signs of malignancy were often overlooked, likely due to limited awareness that leukemias/lymphomas can present similarly to periapical conditions. Therefore, it is crucial to maintain a high level of vigilance to prevent diagnostic delays and misdiagnosis, as well as optimize treatment outcomes for patients. Future multicenter studies are necessary to gain a better understanding of these malignancies in endodontic settings and to explore the effectiveness of targeted continued educational initiatives for clinicians to improve their capabilities for the precise diagnosis of conditions, consequently, enhancing patient outcomes.

Limitations of this review include its reliance on data from case reports and small case series, as cohort studies are scarce given the rarity of leukemia/lymphoma in the periapical region. As a result, it is difficult to ascertain whether these reports fully represent the spectrum of clinical experiences, introducing the possibility of selection bias. Despite the challenges inherent in publishing case reports, these studies remain valuable for understanding rare and well-documented diseases, particularly their oral manifestations[72]. We recommend that future research provide more detailed descriptions of affected individuals, following-up lesion progression over time and reporting associated outcomes to better inform clinical practitioners.

In summary, due to the rarity of leukemia/lymphoma, endodontists may not be familiar with these malignancies, which can mimic periapical conditions due to similar clinicoradiographic features. This overlap increases the risk of inappropriate endodontic treatments and delays in diagnosis, potentially worsening disease prognosis and patient outcomes. To mitigate these risks, endodontists should remain vigilant and incorporate these hematolymphoid malignancies into the differential diagnosis of periapical conditions. Continuous education on the latest diagnostic criteria and collaboration with other healthcare professionals can enhance diagnostic accuracy and ensure timely and appropriate patient management.

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The authors deny any conflicts of interest related to this study.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version at www.jendodon.com (https://doi.org/10.1016/j.joen.2024.11.005).

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