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REVIEW ARTICLE

Clinicodemographic features, management, and recurrence rates of aneurysmal bone cysts of the jaws: a systematic review

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Abstract:

Objective: To carry out a systematic review of available data of aneurysmal bone cyst (ABC) of the jaws. **Methods:** The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. A systematic search until in four databases and grey literature was conducted. As eligibility criteria, case reports and case series describing the clinicopathological and management of ABC were included. The quality assessment of the studies was performedby the Joanna Briggs Institute's (JBI) tool. **Results:** A total of 190 studies reporting 257 cases were evaluated. ABCs affected females slightly more (53.9%), with a mean age of 19.7 years. In 64.4% of cases, no history of trauma was reported. Most lesions were symptomatic (53.2%) and located in the posterior mandible (77.8%). Clinically, they appeared as firm swellings or nodules (95.8%). Multilocular (67.9%) radiolucency (87.4%) was the predominant radiographic feature. Marginal or segmental resection was the most common treatment (34.2%), and 86.4% of patients had no recurrence. While case reports adhered well to JBI guidelines, case series often lacked demographic detail and participant selection criteria. **Conclusion:** ABCs of the jaws predominantly affect young individuals without a marked gender predilection and are most frequently located in the posterior mandible.

Keywords: Aneurysmal bone cysts, Jaw, Pseudocyst, Maxilla.

INTRODUCTION

Aneurysmal bone cysts (ABC) are benign intraosseous, osteolytic, expansive and hemorrhagic lesions. Only 1-3% of ABCs occur in the head and neck region, with the jawbones most commonly affected[1,2]. These lesions can enlarge rapidly, affecting bone structure and subsequently leading to pathological fractures[3]. Even though the pathogenesis of ABC is still unclear, one of the theories raised proposes that the lesion may be of a reactive nature caused by a circulatory abnormality leading to increased venous pressure and resulting in subsequent dilation of the vascular network[4]. Intraosseous or subperiosteal hemorrhage may activate osteoclasts and induce bone resorption and local remodeling. This theory is no longer accepted for primary ABC, which involves rearrangement of the USP6 oncogene at chromosome 17, but remains plausible for secondary ABC, which does not show this translocation[5].

Statement of Clinical Significance
This systematic review of 257 aneurysmal bone cysts (ABCs) of the jaws, uncommon lesions that predominantly affect young individuals, summarizes their characteristic diagnostic patterns. Early recognition of firm swellings in the posterior mandible, where most lesions arise, supports timely and appropriate therapeutic planning, helping to reduce recurrence and minimize the need for aggressive surgical procedures.

In general, the majority of ABC cases occur up to the age of 20 years[5]. Although they tend to occur more in females, Richardson et al.[3] have reported absolutely no gender predilection, with the cases being evenly distributed between males and females. ABC mostly affects the vertebral column and the metaphysis of the long bones. Clinically, jawbones ABCs (JABC) may present as a symptomatic or asymptomatic swelling, with limitation

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of mouth opening, paresthesia, tooth displacement, root resorption, toothache, and pathologic bone fracture[6,7]. Radiography reveals classic osteolytic lesions, whereas magnetic resonance image (MRI) reveals blood-filled lesions and fluid-fluid levels[3]. The main differential diagnoses are malignant tumors, ameloblastomas and central giant cell lesions[8], lesions with clinically and radiographically aggressive behavior. For diagnostic purposes it is essential that a biopsy be performed for histopathological examination, with an excisional or incisional biopsy being then chosen depending on the diagnosis. Histologically, the cavities lack an endothelial lining and are filled with blood. They are surrounded by fibrous septae, enclosing fibroblasts, inflammatory cells, siderophages, and osteoclastic giant cells[5]. Currently, the mainstay of treatment for ABCs is conservative surgical intervention including excision, curettage, and bone grafting. Cases with greater involvement of adjacent structures may require a more invasive intervention such as resection[9]. Recurrence is low, but repeated recurrences may occur due to the incomplete removal of the lesion. To the best of our knowledge, no systematic review regarding ABC of the jaws has been conducted in the literature so far. Thus, the objective of the present study was to integrate the available data published in the literature on ABC of the jaws into a systematic review of the clinicodemographic features, treatment and recurrence frequency of this condition.

MATERIAL AND METHODS

Search strategy

The search was performed independently by two examiners in the following electronic databases: PubMed, Web of Science, Scopus, and EMBASE. Also,gray literature was assessed by Google Scholar and ProQuest. The search was conducted up to November 2023, without year restriction. Search strategy was constructed using the most cited descriptors in previous articles combining Medical Subject Heading (MeSH) terms and text words with Boolean operators "AND" and "OR", with adaptation to the syntax rules of each database. The search strategies applied to each database and the findings obtained are summarized in Supplementary Table 1. An additional manual search of the reference lists of the selected studies was performed. All articles selected were imported into the EndNote Web© (Clarivate Analytics) reference manager to catalogue the references.

Eligibility criteria

The inclusion criteria for the present systematic review concerned case reports and case series describing patients diagnosed with ABC of the jaws according to the criteria of the World Health Organization[10]. The outcomes of interest were age, sex, anatomical location, history of trauma, and treatment.

Exclusion criteria were articles and conference abstracts, animal studies, systematic reviews, and studies that were neither case reports or case series. In addition, articles that met the following criteria were excluded

1. Not ABC;
2. Not in gnathic bones (maxilla or mandible);
3. Language other than English;
4. Not appropriate study design;
5. Article not found;
6. Not appropriate study design; and
7. ABC occurring in animals.

Study selection

All stages were performed by two independent authors. The first stage consisted of searching each database, duplicates were removed automatically by Endnote and then manually by reviewers and evaluating the titles and abstracts of the selected studies. When it was not possible to analyze the studies based on title and abstract, the full text was assessed and read for the final decision. The second stage consisted of reading the full texts of the potentially eligible studies according to the eligibility criteria. Disagreements on study inclusion were solved by consensus with a third author.

Data extraction

Data extraction was performed independently by two authors. Disagreements were solved by a third author. The following data were extracted from the included studies: author name(s), year of publication, country, age, sex, patient clinical condition, anatomical location, fundamental lesion, consistency, color, borders' definition, surface, mobility, other clinical signs, aspiration content, reported symptoms, duration of symptoms, being a primary or secondary lesion; associated lesion (when secondary); radiological features, imaginological exams performed, history of trauma, other possible causes; diagnostic hypotheses; type of biopsy; histopathological features; treatment, transoperatory event, recurrence, period of recurrence; follow-up.

Table 1. Detailed descriptions of the included studies.

	n (%)
Continent (n=190)	
Asia	86 (45.3)
Europe	47 (24.7)
America	46 (24.2)
North America	31 (67.4)
South America	15 (32.6)
Oceania	6 (3.2)
Africa	5 (2.6)
Sex (n=256)	
Female	138 (53.9)
Male	118 (46.1)
Age, in years (n=231)	
Mean (SD)	19.7 (12.8)
Range	2–73
Patient clinical condition (n=101)	
Unremarkable	85 (84.2)
Fever	3 (3.0)
Pregnancy	3 (3.0)
Lymphadenopathy	3 (3.0)
Asthma	2 (1.9)
Lymphoma	2 (1.9)
Allergy	1 (1.0)
Anemia	1 (1.0)
Rheumatic fever	1 (1.0)
History of trauma (n=90)	
No	58 (64.4)
Yes	32 (35.6)
Duration of symptoms, in weeks (n=124)	
Mean (SD)	25.3 (30.7)
Range	0.4–156
Symptomatology (n=228)	
Yes	122 (53.5)
Pain	70 (57.4)
Tender	33 (27.0)
Paresthesia/hypoesthesia	16 (13.1)
Local heat/warmth/burning	3 (2.5)
No	106 (46.5)
Anatomical location* (n=266)	
Mandible	207 (77.8)
Posterior mandible	193 (93.3)
Anterior mandible	14 (6.7)
Maxilla	48 (18.0)
Posterior maxilla	32 (66.7)
Anterior maxilla	16 (33.3)
Maxillary sinus	10 (3.8)
Mandibular condyle	1 (0.4)

Continue...

Table 1. Continuation.

	n (%)
Fundamental lesion (n=216)	
Swelling/nodule	206 (95.4)
No clinical signs	10 (4.6)
Consistency (n=124)	
Hard/firm/rigid	105 (84.7)
Soft	9 (7.3)
Crepitus	8 (6.4)
Rubbery	2 (1.6)
Color (n=67)	
Normal/color of the mucosa/color of the skin	48 (71.6)
Red/reddish/erythematous	17 (25.4)
White/whitish	1 (1.5)
Dark	1 (1.5)
Borders (n=66)	
Well-defined/circumscribed	37 (56.1)
Ill-defined/diffuse	27 (40.9)
No borders (no clinical sign)	2 (3.0)
Surface (n=37)	
Smooth surface	28 (75.7)
Rough surface	9 (24.3)
Mobility (n=23)	
Fixed	17 (73.9)
Fluctuant	6 (26.1)
Other clinical signs (n=128)	
Facial asymmetry	73 (57.0)
Trismus/limited jaw opening	33 (25.8)
Nasal cavity obstruction	8 (6.2)
Tooth mobility	7 (5.5)
Nasal cavity bleeding	3 (2.3)
Eye protrusion	2 (1.6)
Fracture	2 (1.6)
Primary/Secondary Lesion (n=235)	
Primary	179 (76.2)
Secondary	56 (23.8)
Imaginological examinations performed* (n=360)	
Panoramic radiograph	149 (41.4)
Computed tomography	124 (34.4)
Magnetic resonance imaging	36 (10.0)
Other	23 (6.4)
PA radiograph (skull)	15 (4.2)
Angiography	13 (3.6)

Continue...

Table 1. Continuation.

	n (%)
Radiological features	
Internal appearance (n=198)	
Radiolucent/hypodense	173 (87.4)
Mixed	19 (9.6)
Radiopaque/hyperdense	6 (3.0)
Locularity (n=168)	
Multilocular	114 (67.9)
Unilocular	54 (32.1)
Other radiological features (n=259)	
Cortical expansion	131 (50.6)
Well to moderately defined margins/borders/contours	53 (20.5)
Root resorption	25 (9.6)
Ill-defined margins/borders/contours	21 (8.1)
Cortical perforation	20 (7.7)
Scalloped borders	6 (2.3)
Sclerotic borders/rim	3 (1.2)
Aspiration (n=75)	
Blood/red fluid	62 (82.7)
No fluid withdrawn	7 (9.3)
Other	4 (5.3)
Yellow/citrine fluid	2 (2.7)
Diagnostic hypothesis (n=213)	
Aneurysmal bone cyst	51 (23.9)
Odontogenic tumor	41 (19.3)
Giant cell granuloma	34 (15.9)
Fibro-osseous and osteochondromatous lesions	21 (9.9)
Intraosseous/central hemangioma or Arteriovenous Malformations	13 (6.1)
Carcinomas or Sarcomas	12 (5.6)
Odontogenic cysts	12 (5.6)
Others	9 (4.3)
Simple bone cyst	7 (3.3)
Malignant (no other specification)	4 (1.9)
Benign maxillofacial bone and cartilage tumours	3 (1.4)
Benign (no other specification)	3 (1.4)
Osteomyelitis	2 (0.9)
Central neural lesions	1 (0.5)
Biopsy (n=168)	
Incisional	88 (52.4)
Excisional	80 (47.6)

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Table 1. Continuation.

	n (%)
Treatment (n=234)	
Marginal or Segmental resection	80 (34.2)
Curettage	75 (32.1)
Enucleation	57 (24.4)
Embolization	9 (3.8)
Drug therapy (systemic)	4 (1.8)
Radiotherapy	2 (0.8)
Cryotherapy	2 (0.8)
None (follow-up only)	2 (0.8)
Other	2 (0.8)
Esclerotherapy	1 (0.5)
Trans-surgery event (n=103)	
Uneventful	68 (66.1)
Bleeding/hemorrhage	35 (33.9)
Recurrence (n=169)	
No	146 (86.4)
Yes	23 (13.6)
Period of recurrence, in months (n=26)	
Mean (SD)	17.7 (22.1)
Range	1–96
Follow-up, in months (n=145)	
Mean (SD)	27.9 (41.3)
Range	0.2–408

*In some cases, more than one anatomical location or imaginological exam were reported.

Qualitative assessment

Quality was assessed by two independent authors to determine the risk of bias of each study. Whenever differences occurred, a third author was consulted. Quality assessment was conducted according to the Joanna Briggs Institute — University of Adelaide tool for case reports or case series[11]. The included cases reports were assessed in terms of the following domains: clear description of patient's demographic characteristics, medical history and current clinical condition, clear description of the propaedeutic data, treatment, post-intervention clinical condition, adverse events, and lessons provided by the case report. In the case series, information was collected on criteria for inclusion, condition measured, methods for identification, inclusion of participants, demographics and clinical information of participants, follow up and analysis statistics.

Data synthesis

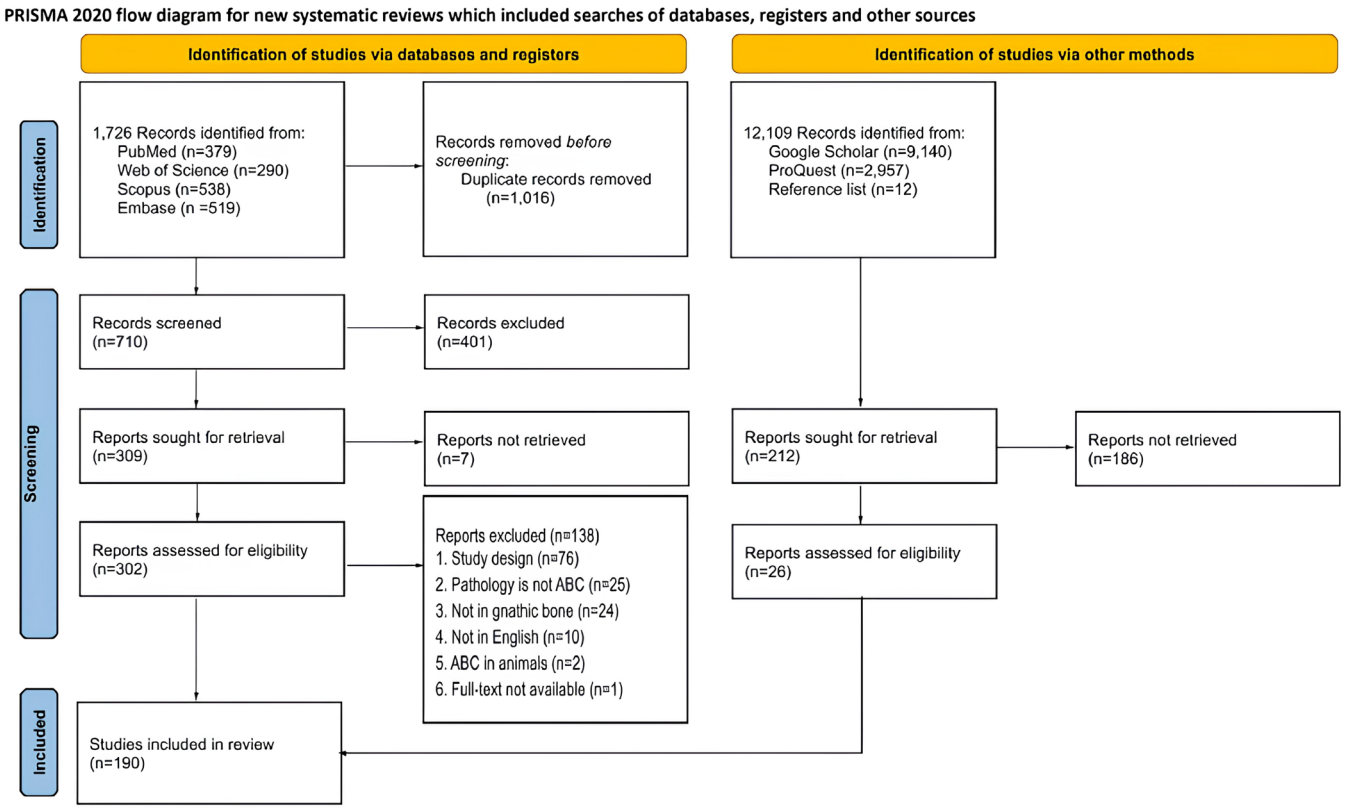
The data synthesis process involved a meticulous summary of the extracted variables and analysis of information from the selected studies. Utilizing a systematic approach, we employed a narrative synthesis to integrate and interpret the diverse data sets. The data were tabulated and processed using Microsoft Excel®.

RESULTS

Study selection

The flowchart according to the PRISMA 2020 statement illustrating the process of search and selection of the studies from this systematic review is presented in Figure 1.

A total of 1,726 potentially relevant records were gathered from the electronic databases. After duplicate removal, 710 records were examined based on their titles and abstracts. Of these, 401 were excluded since they did not meet the eligibility criteria. A total of 302 full-text articles were then evaluated and 138 were excluded according to the reasons presented in the flow diagram. A total of 12,109 potentially relevant



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Figure 1. PRISMA 2020 flow diagram illustrating the selection process of studies included in the systematic review[18].

records were identified from the gray literature, along with 12 additional records from a manual search of the bibliographies of the included studies. After applying the inclusion and exclusion criteria, 26 studies were selected for inclusion. Finally, a total of 190 studies reporting a total of 257 cases of JABCs were included in this systematic review. All included articles are listed in Supplementary Table 2.

General characteristics of included studies

The majority of studies were reported in Asia (45.3%), followed by Europe (24.7%), America (24.2%), Oceania (3.2%), and Africa (2.6%) (Figure 2).

The included studies covered all continents, encompassing 38 different countries. The country with the highest number of publications was India with 53 publications (27.9%), followed by the United States with 27 (14.2%) and Brazil with 11 (5.8%). The case reports were published between 1958 and 2025, with more than half of them published from 2011 onwards. General descriptions of the included studies are summarized in Table 1.

Some variables were poorly provided and for this reason the number of cases and data available did not match. Similarly, some case reports provided more than one information item for the variable collected, so that the total quantity of data may have been greater than the number of cases of the present review.

Regarding the description of the sample, women were slightly more reported (53.9%) and mean patient age was 19.7 years. Most patients (84.2%) did not have relevant prior medical conditions. About etiology, 64.4% of patients reported no history of trauma. Although 53.5% of the cases were symptomatic, pain (57.4%) and tenderness (27.0%) were the most common symptoms reported. The most common location of ABC was the posterior mandible, followed by posterior maxilla and the anterior area of the maxilla. The clinical presentation of the lesion was reported as a swelling/nodule (95.4%) of firm consistency (84.7%) (Figure 3), without color change (71.6%), with a smooth surface (75.7%) and fixed (73.9%). Other signs exhibited by the individuals reported were facial asymmetry (57.0%) and trismus (25.8%), among others (Figure 3).

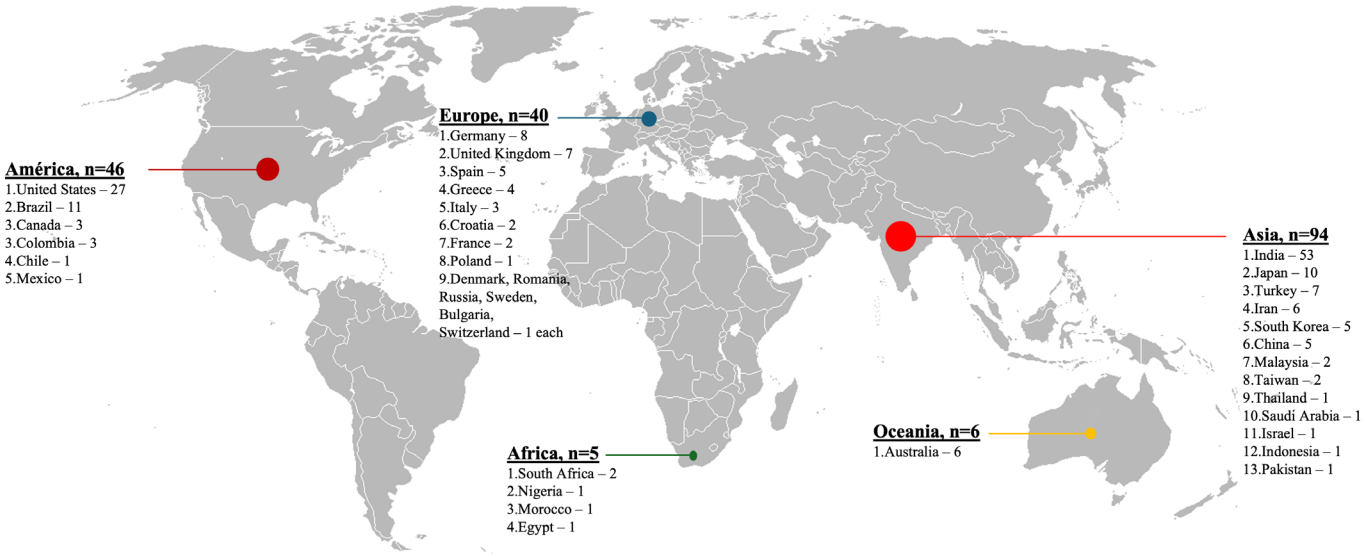


Figure 2. Global distribution of included articles. Map showing the distribution of publications by continent. Each colored circle represents the continent, with its size proportional to the total number of studies. The accompanying lists detail the number of publications per country within each continent, with the circle placed on the country that contributed the highest number of studies.

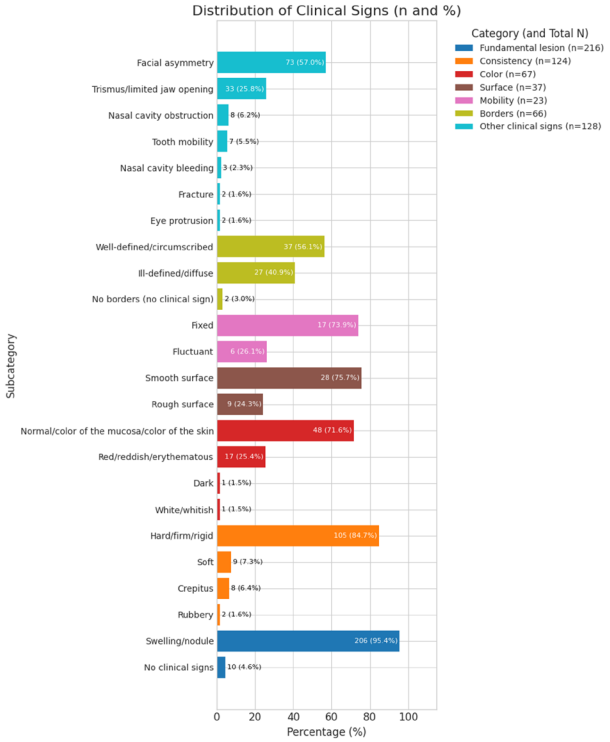


Figure 3. Summary of clinical aspects reported in the studies.

During the diagnostic process, aspiration of the lesion was reported in 75 (29.2%) cases and the aspirated fluid was most often identified as blood (82.7%). The lesion was identified as primary in 76.2% of cases. The imaging exam most frequently used for diagnosis was panoramic radiography (41.4%), followed by computed tomography (34.4%). The lesion was identified radiologically as radiolucent (87.4%), being described as multilocular (67.9%) in most reports (Figure 4). Other radiographic findings reported were cortical expansion (50.6%), well-defined contours (20.5%), and root resorption (9.6%).

Regarding the differential diagnoses most frequently raised, ABC (23.9%) were the most mentioned, followed by odontogenic tumors (19.3%) and giant cell granulomas (15.9%), among others. An incisional biopsy was indicated in 52.4% of cases and an excisional biopsy was indicated in another 47.6%. Histopathologically, an ABC usually consists of a fibrous connective tissue stroma with blood-filled sinusoids, multinucleated giant cells, and irregular osteoid. For treatment purposes, marginal or segmental resection was the procedure most frequently performed (34.2%), followed by curettage (32.1%) and lesion enucleation (24.4%). Intraoperative events were reported in 35 cases, 33.9% of which were related to hemorrhage.

A total of 169 reports provided information about lesion recurrence. Among these, the recurrence rate was 13.6%, with a mean period of 17.7 months and a mean follow-up of 27.9 months.

Quality assessment

The critical appraisal of the case reports revealed that all articles provided a clear description of the patients'

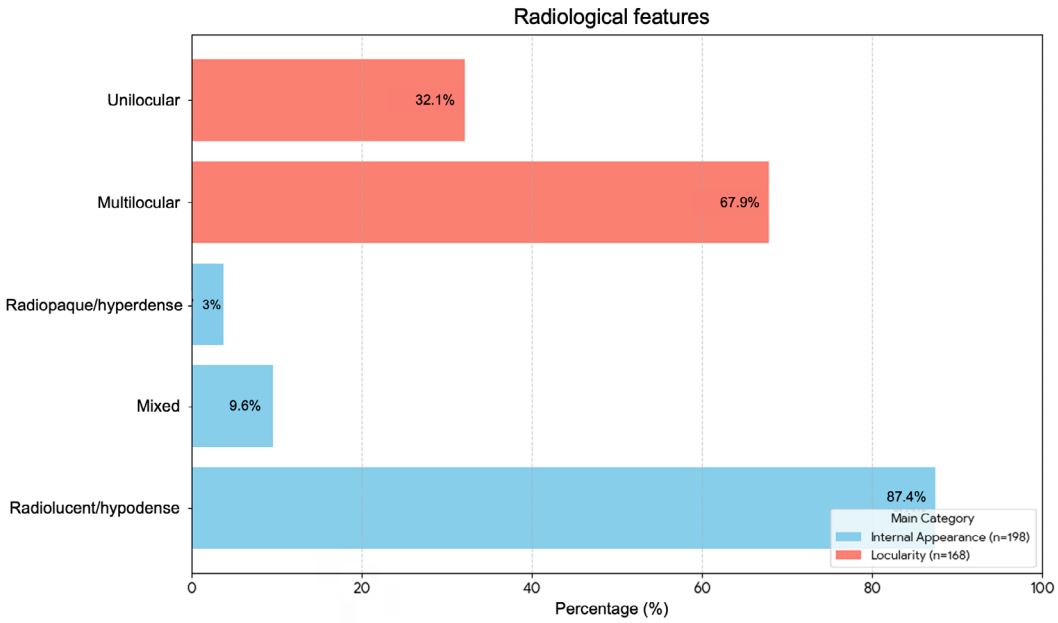


Figure 4. Radiographic features.

demographic characteristics. In 96.5% of the cases, a clear account of the patient's medical history and timeline was presented. The current clinical condition was clearly described in 83.2% of the reports. Furthermore, 88.4% of the articles demonstrated clarity in the description of diagnostic tests, evaluation methods, and results obtained. Therapeutic interventions or procedures were clearly described in 94.2% of the cases. The condition under which the intervention was performed was reported in 89.0% of the cases, and adverse events were mentioned in 89.0% of them. Finally, 86.7% of the articles included relevant takeaway lessons. Regarding the critical appraisal of the case series, 94.1% of the articles clearly defined the criteria for inclusion. In all cases, the condition was measured in a standardized and reliable manner for all participants. Valid methods were used to identify the condition in 94.1% of the studies. However, only 5.9% of the articles reported consecutive and complete inclusion of participants. Clear reporting of participants' demographic data was observed in just 23.5% of the articles, while clinical information was clearly presented in 70.6% of them. Outcomes or follow-up results were adequately reported in 64.7% of the studies. Lastly, information regarding the presenting site(s) or clinic(s) was clearly reported in only 11.7% of the articles.

DISCUSSION

ABC is a common skeletal bone lesion usually observed in long bones and vertebrae. However, its occurrence in jawbones is rare[1]. The present systematic review identified 190 articles of JABC, for a total of 257 cases published between 1958 and 2025. Most cases were from India, followed by the United States and Brazil. Our findings revealed slightly women predilection and a mean age at diagnosis of 19.7 years, in agreement with the literature. Recently, Richardson and colleagues (2022)[3] obtained similar results in a review of 72 head and neck ABC cases, *i.e.*, mean patient age of 19.1 years and cases evenly distributed between males and females[3].

The posterior mandible was the most affected site reported by the authors included in our study, with swelling or a nodule described in almost all cases. Most cases were symptomatic, with several patients reporting pain and tenderness. In several cases published in the literature, ABC is also an asymptomatic lesion, occasionally discovered as radiolucency in routine radiographies[1]. In the present systematic review, the imaging exam most frequently used for diagnosis was panoramic radiography, followed by computed tomography. Radiographic findings showed that the most common presentation was a radiolucent and multilocular lesion, in agreement with the current literature[1].

Most of the reports included in this review suggested that ABC is a primary lesion (76.2%), in agreement with the published literature[12]. However, ABC may be associated with other lesions such as giant cell tumors and osteoblastomas. In the current review,

associations were found in 59 (22.9%) cases. Although some evidence indicates that ABC is a reactive processor, recent studies propose that this lesion has an associated tumor pathogenesis[13,14]. The history of local trauma is still one of the main factors associated with the development of ABC[15]. In the present study, only 90 articles reported an investigation of the association of ABC with trauma, and only 32 patients (35.6%) could recall a history of trauma.

Due to the absence of an epithelial lining, ABC is considered to be a pseudocyst[15]. Morphologically, it usually consists of a fibrous connective tissue stroma with blood-filled sinusoids, multinucleated giant cells, and irregular osteoid.

Three different patterns are described in the literature:

1. Vascular;
2. Solid; and
3. Mixed[1].

The first type consists of loose stroma and numerous engorged blood-filled sinusoids, with risky bleeding very commonly observed during surgery, plus extensive bone destruction with spread to soft tissues. The second type consists of dense fibrous stroma and few blood vessels, without severe bleeding during surgery. The third, mixed type lies somewhere between the previous two variants. However, the patterns of ABC were not clearly described in the included studies.

Although ABC does not show histological similarity to other cysts, its clinical and radiographic characteristics may challenge clinicians in the diagnosis. Regarding differential diagnoses, ABC may resemble malignant lesions due to its invasive, destructive and fast-growing characteristic[13]. In the present study, malignant lesions were hypothesized in 7.5% of cases. However, odontogenic tumors (19.3%) and central giant cell lesions (15.9%) represented the most cited possible diagnoses. In fact, odontogenic tumors such as ameloblastomas and odontogenic keratocysts[8] resemble ABC due to their radiolucency and locularity characteristics as well as their aggressiveness. The similarity between ABC and central giant cell lesions is related to their aggressive and expansive behavior, as well as their common location in the mandible[16].

For diagnostic purposes, associated with the clinical history and imaging tests, it is essential that a biopsy be performed for histopathological examination. There is a similar distribution of types of biopsies, with the choice being based on diagnostic hypotheses, lesion extension and professional experience. Both excisional and incisional biopsies should provide histological evaluation of the lesion for diagnosis. In this review, similar proportions of excisional and incisional biopsies were reported, probably owing to the wide range of clinical characteristics that ABC may exhibit. Also, the clinical hypotheses raised showed that, in most cases, ABCs resemble lesions of indolent behavior. However, clinicians might prefer to be more cautious and perform incisional biopsies when malignant lesions cannot be definitely excluded from the diagnostic hypotheses.

While the treatment for ABC can be surgical or non-surgical[9], surgical intervention is the gold-standard approach to this lesion. A recent review of head and neck cases showed that surgery was performed in 94.1% of cases[3], with similar findings being obtained in the present study, in which surgical procedures were the most frequent. In addition to surgical interventions, embolization, drug therapy, radiotherapy, and chemotherapy are also forms of nonsurgical treatment, representing less than 10% of the sample[3]. In cases with the lowest recurrence rates, *en bloc* resection has been considered as an approach. However, this method has been more extensively studied in long bones than in the head and neck region which usually requires more delicate interventions[17].

While our systematic review offers a thorough consolidation of existing evidence, it is crucial to recognize and tackle specific limitations, especially concerning the incorporation of case reports and case series. The utilization of these study types introduces inherent biases, including publication bias and the possibility of selective reporting. In this sense, during the extraction of articles, lack of details was observed in the case reports, hindering a global analysis during the review. Some variables considered important by the authors, such as a history of local trauma as mentioned above, were found in a small number of publications. Also, systematic reviews of clinical cases should always consider publication bias, which involves a predominance of serious and successful published cases that may not represent the case series as a whole. Finally, limitation to reports in the English language may also have influenced the results obtained, underestimating their prevalence. For future research, it is suggested that the history of the lesion, clinical and radiographic aspects, and information regarding the treatment and follow-up of the lesions be reported in detail.

CONCLUSION

In summary, this study evaluated 190 articles for a total of 257 cases, showing that slight female

predilection (53.9%), with a mean age of 19.7 years, and most often occurs in the posterior region of the mandible. Approximately two-thirds of the reported cases were considered to be primary lesions. Despite its aggressive behavior, the mean recurrence found was relatively low, probably associated with more invasive treatments such as resection of the lesion with margins. This review seeks to assist health professionals regarding the diagnosis and treatment of ABC.

Other information

Protocol and registration

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) recommendations[18] and was registered in the PROSPERO database (CRD42020215871).

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AUTHORS' CONTRIBUTIONS

LCJ.: Conceptualization, Investigation, Methodology, Writing – original draft. GSL: Investigation, Methodology. BBS: Investigation, Methodology. JLS: Investigation, Methodology. RAZ: Investigation, Methodology. ACS: Investigation, Methodology. FMS: Methodology, Writing – review & editing. WVH: Writing – review & editing. LFS: Methodology, Writing – review & editing. MDM: Supervision, Writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Ethics approval: All procedures followed the ethical standards of the Helsinki Declaration of 1975, as revised in 2008.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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