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REVIEW

Papilliferous Keratoameloblastoma

Systematic review

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abstract: Papilliferous keratoameloblastoma (PKA) is a rare entity, and not much is known about its clinicodemographic features or biological nature. This review aimed to provide clarity regarding the characterisation of the demographic, clinical, radiological and histopathological features of PKA. Case reports of PKA were identified through a systematic search across multiple databases. The search yielded a total of 10 cases, half of which were of Indian origin. All the cases invariably occurred in the mandibular posterior region and involved the right side; only one case primarily involved the left side of the mandible. PKA should be considered a variant of the conventional ameloblastoma that is towards the more aggressive end of the spectrum. It tends to occur in older individuals (in their fifth decade or older), with a marked propensity to occur in the right mandibular posterior region. Surgical resection with diligent follow-up is warranted in the treatment of PKA.

Keywords: Odontogenic Tumors; Ameloblastoma; Keratin; Odontogenic Keratocyst.

An array of metaplastic changes can occur in the epithelial component of ameloblastoma (AM) that are attributable to the potentiality of the odontogenic epithelium. The epithelial cells within ameloblastic follicles or plexuses may exhibit squamous, basaloid, granular and clear cells or even mucous metaplasia. These metaplastic changes give rise to a polymorphic histopathological picture in AM. Consequently, numerous corresponding variants of AM, such as acanthomatous, basaloid, granular and clear cell, have been recognised.[1]

Squamous metaplasia in the central stellate reticulum-like cells of AM is the hallmark of acanthomatous ameloblastoma (AA). The terminal fate of squamous cells is to form keratin and desquamate. As a result, extensive keratinisation to the extent of keratin pearl formation may occur in AM. The following four types of histopathological pictures have been reported in terms of the spectrum of keratinising AMs: 1) simple histology: ameloblastomatous follicles centrally filled with ortho- or para-keratin; 2) simple histology along with features of conventional odontogenic keratocyst (OKC); 3) complex histology: extrusion of keratin masses into the stroma along with features of simple histology with or without hard tissue formation; and 4) papilliferous histology: papillary projections of the odontogenic epithelium into the cystic lumen or microcystic spaces.[2]

In 1992, the World Health Organization (WHO) recognised AM with extensive keratinisation as keratoameloblastoma (KA). While some authors consider KA as a subset of AA, others have reported it as a distinct variant of AM.[2,3] The centrally desquamated cells lead to the formation of microcystic areas within the ameloblastomatous follicles. The presence of papillary ingrowths of odontogenic epithelium within these microcysts or in the primary cystic lumen is an even rarer phenomenon. The first such case was described by Pindborg and Weinmann as a subset of AM, and the term 'papilliferous keratoameloblastoma' (PKA) was suggested.[4] While numerous cases of KA displaying either simple or complex histology have been identified, the PKA variant is exceedingly rare.[3,5] As a result, not much is known about the clinicodemographic characterisation and biological nature of PKA.

The question of whether PKA differs from other variants of AM in its biological behaviour or if it belongs to the spectrum of AA without any clinical significance remains unknown. The present systematic review aimed to gain a better understanding of this rare entity by identifying and analysing all reported cases of PKA in the scientific literature. The objectives of this review were to describe the demographic, clinical and histopathological characteristics of PKA.

Methods

Case reports of PKA were retrieved through a systematic search of the following databases: Ovid MEDLINE (Wolters Kluwer, New York, USA), PubMed (National Library of Medicine, Maryland, USA), PubMed Central (National Library of Medicine), Web of Science Citation Index Expanded (Clarivate, Philadelphia, USA) and Google Scholar (Google, California, USA). A systematic search with keywords ([ameloblastoma] and [papillae]) or

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(papilliferous ameloblastoma) was conducted. An additional search with keywords ([ameloblastoma] and [keratin]) or (keratoameloblastoma) or (keratinising ameloblastoma) was performed and screened for the potential presence of papilliferous areas in the microscopic picture. The cross-references cited in the retrieved literature were also screened for the identification of possible cases of PKA, in case any were missed by the search strategy.

Complete text articles of all cases belonging to the spectrum of keratinising AMs were scrutinised for histopathological features of PKA. The quality of the case reports was evaluated by employing the Joanna Briggs Institute critical appraisal tool for case reports.[6] To further minimise bias in quality assessment, the authors were divided into two groups (SS and TC; MS and YA), and they independently evaluated the case reports for inclusion in this review [Figure 1].

The criteria for inclusion of the cases constituted the histopathological presence of papilliferous proliferations of the odontogenic epithelium into the primary cystic lumen or the formation of microcysts within the AM follicles along with the formation of keratin [Figure 2].

For a better understanding of the histopathological features, photomicrographs can be found in the case reported by Bedi *et al*.[2]

Cases with an ambiguous description or unclear histopathological demonstration of a papilliferous component or keratin formation were excluded from the review. The presence or absence of additional histopathological features besides papilliferous patterns, such as budding of cells, dentinoid formation, calcifications, ghost cells or OKC-like features, were also recorded. However, these additional features were not considered definitive criteria for diagnosis of PKA as they represent variations that can occur in the odontogenic neoplasm.

DATA EXTRACTION

The demographic, clinical, radiological and histopathological features of all the cases were extracted. Additional investigations such as those for special stains, immunohistochemistry (IHC) or gene expression were also performed. The treatment performed in all the cases, number of recurrences, period between the recurrences and duration with no evidence of disease after treatment were recorded. The quality of articles included in the review was also assessed utilising the Grading of Recommendations Assessment, Development and Evaluation approach.[7] The extracted data were entered and tabulated into worksheets (Microsoft Office Excel 2016, Redmond, Washington, USA).

The review title and search protocol are registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42021282930).

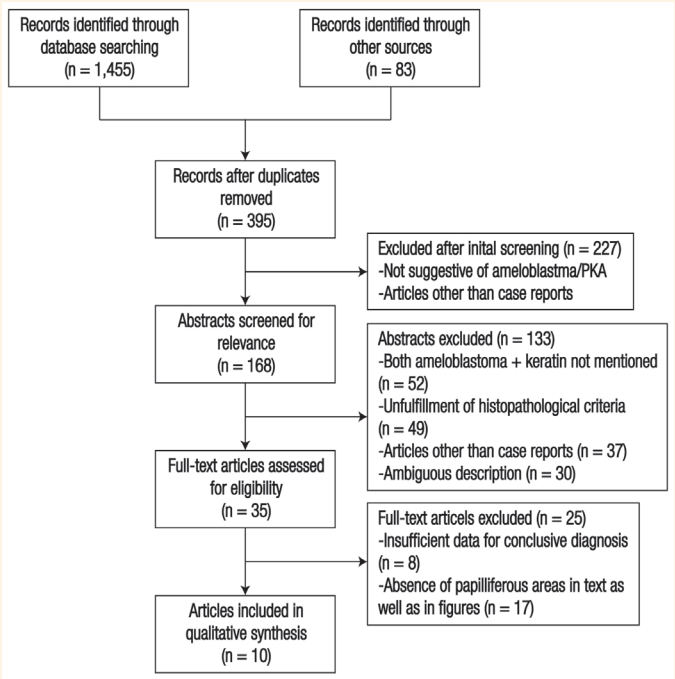

Figure 1: PRISMA flow chart showing the selection process of articles for the final qualitative synthesis of the present systematic review.
PKA = papilliferous keratoameloblastoma.

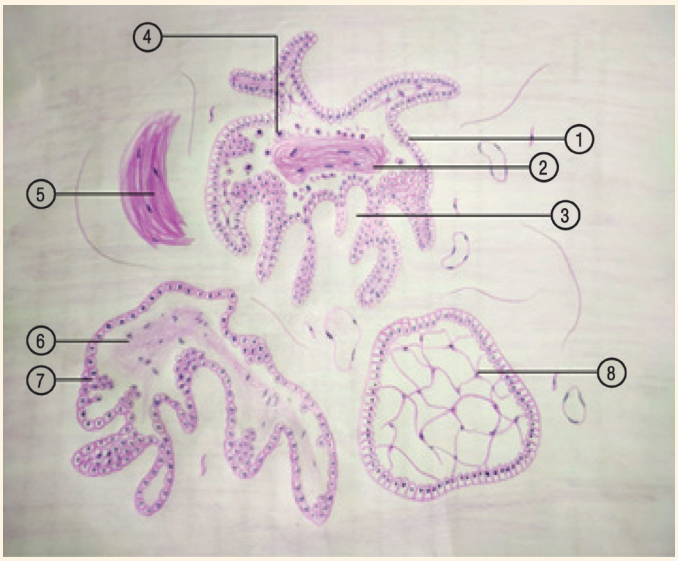

Figure 2: Line diagram illustrating the histopathological features of PKA. Ameloblast-like cells (1), stacks of keratin within cystic degeneration in the follicle (2), papillary projections into the follicle (3), acantholytic cells (4), keratin extruded into the stroma (5), necrotic material within the follicle (6), micropapillary structures in a follicle lined by squamous epithelial cells (7) and normal ameloblastoma-like follicle with central stellate reticulum-like cells (8).
PKA = papilliferous keratoameloblastoma.

Results and Discussion

A total of 10 reported cases of PKA were found in the scientific literature available in English [Table 1].[2–5,8–13] Half of the patients (n = 5, 50%) in these reported cases were of Indian origin.[2,5,11–13] The age of patients ranged from 18 to 76 years, with a mean age of 49.7 ± 20.95 years. In their review, Bedi *et al*. reported a slightly lower mean age of 40 years for patients presenting with KA exhibiting papilliferous features.[2] Conventional AM shows a peak of occurrence in the third and fourth decades.[1,14] However, the cases of PKA were evenly distributed among all the decades, with a majority of cases occurring in the fifth decade or later (n = 7, 70%). Only three cases occurred in patients aged >30 years, while no case of PKA occurring in the fourth decade has yet been reported. These findings indicate that PKA may occur at any age but commonly occurs in patients of older age groups.

A slight male predilection was observed, with 60% of the cases occurring in males (n = 6) and 40% in females (n = 4). The male-to-female ratio was found to be 1.5:1. Data from a recent systematic review of the global profile of AM suggests that conventional AM also exhibits a slight male predilection in Africa, North America and Asia.[15] A higher male predilection with two-thirds of cases occurring in males was reported by Konda *et al*., and a ratio as high as 3:1 was discovered by Bedi *et al*. in their respective reviews of PKA.[2,12] On the contrary, an equal sex distribution (1:1) in reported cases of PKA was highlighted by Rathore *et al*.[13] However, the omission of certain cases or reports of additional cases after the reviews were conducted by these authors has led to a variation in the sex distribution of PKA.

Almost all patients (n = 9; unknown for one case) complained of swelling of duration ranging from three months to five years. The swelling was asymptomatic in most cases (n = 6, 60%) which is a common mode of presentation of AM. Pain was present in three cases, while mobility of teeth was present in one case. Pain is an uncommon feature in AM, usually noted in lesions of larger size that tend to impinge on adjacent or involved nerves, or is a result of secondary infection.[16] Infiltration of lesions into the bony trabeculae and subsequent resorption could account for the occasional mobility of teeth noted in conventional AM or its variants, such as PKA. Difficulty in mandibular movement was present in the case reported by Collini *et al*., which was attributable to the involvement of the condyle by the lesion.[10]

All cases invariably involved the posterior region of the mandibular jaw (n = 10, 100%); none of the reported cases of PKA to date have primarily occurred in the maxilla or anterior region of the mandible. This propensity of PKA to occur in the mandible is similar to that displayed by conventional AM, wherein 90% of cases involve the mandibular jaw.[17] The lesion exhibited a marked predilection to occur on the right side (n = 9, 90%), while only one case primarily involving the left side of the mandible was noted. This finding was in contrast to conventional AM, which involves both sides almost equally.[1] In one case, the lesion was extensive enough to involve the entire right

Table 1: Summary of demographic, clinical and radiological features and management of cases of papilliferous keratoameloblastoma (N = 10)[2–5,8–13]

Author and year of publication	**Age in years**	**Gender**	**Nationality**	**Duration in months**	**Jaw**	**Side**	**Region**	**Extent**	**Symptom**	**Radiographic feature**	**Final diagnosis**	**Treatment and** follow-up	GRADE system
Pindborg *et al.*[4] (1958)	57	F	Unknown	Unknown	Mn	Right	Posterior	Body, angle, ramus	Unknown	ML, RL	PKA	Unknown	Low
Altini *et al.*[8] (1991)	76	F	South African	12	Mn	Right	Posterior	PM to sigmoid notch	Swelling	WD, ML, RL	PKA	Hemimandibulectomy 1 year, NED	Moderate
Norval *et al.*[3] (1994)	26	F	South African	60	Mn	Right	Posterior	PM To 3M	Swelling, pain	WD, ML, RL	Unusual variant of KA	Segmental resection + iliac crest graft	High
Takeda *et al.*[9] (2001)	76	M	Japanese	Several	Mn	Left	Posterior	C to 2M, body	Swelling	WD, ML, RL	KA	Surgical resection	High
Collini *et al.*[10] (2002)	62	M	Italian	3	Mn	Right	Posterior	Ramus and condyle	Swelling, difficulty in mandibular movement	Osteolytic lesion with irregular calcifications	PKA	Hemimandibulectomy + modified neck dissection (recurrence after 39 months); resection (recurrence after 18 months); died after 6 years due to concurrent lymphoma	High
Mohanty *et al.*[11] (2013)	46	M	Indian	12	Mn	Right	Posterior	C to ramus	Swelling	ID, ML, RL	PKA	Unknown	Moderate
Bedi *et al.*[2] (2015)	27	F	Indian	7	Mn	Right	Posterior	2PM to sigmoid notch	Swelling	ID, ML, RL	KA complex histology	Wide excision recurred once after 3 years of en bloc resection	High
Konda *et al.*[12] (2016)	44	M	Indian	6	Mn	Right	Posterior	C to 1M	Swelling, intermittent pain, mobility of teeth	WD, UL, RL	Papilliferous keratinising variant of solid multicystic ameloblastoma	In-toto excision 1 year, NED	High
Kuberappa *et al.*[5] (2020)	65	M	Indian	4	Mn	Right	Antero-posterior	31 to 47	Swelling, pain	ID, ML, RL	PKA	Wide excision 2 months, NED	High
Rathore *et al.*[13] (2017)	18	M	Indian	3	Mn	Right	Posterior	C to 3M	Swelling	WD, UL, RL	PKA	Wide excision 2 years, NED	High

F = female; Mn = mandible; ML = multilocular; RL = radiolucency; PKA = papilliferous keratoameloblastoma; PM = premolar; WD = well-defined; NED = no evidence of disease; M = molar; KA = keratoameloblastoma; M = male; C = canine; ID = ill-defined; UL = unilocular.

Table 2: Summary of histopathological features observed in cases of papilliferous keratoameloblastoma (N = 10)[2–5, 8–13]

Author and year of publication	Epithelial component							Connective tissue component	
	Type	Cystic degeneration	Necrotic material	Desquamated keratin	Papillary projections	Ameloblast-like features	Stratified squamous lining in follicles	Extruded keratin	Hard tissue formation
Pindborg *et al.*[4] (1958)	Follicles/ islands	Present	Present	Present	Present	Present	Present	Absent	Absent
Altini *et al.*[8] (1991)	Follicles	Present	Present	Present	Present	Absent	Present	Absent	Absent
Norval *et al.*[3] (1994)	Follicles	Present	Present	Present	Present	Present	Questionable	Present	Dystrophic calcification
Takeda *et al.*[9] (2001)	Follicles	Absent	Absent	Present	Present	Present	Present	Present	Cellular cementum/ woven bone-like
Collini *et al.*[10] (2002)	Nests, tubules, islands, single file	Present	Minimal	Present	Present	Present	Absent	Absent	Absent
Mohanty *et al.*[11] (2013)	Follicles	Present	Present	Present	Present	Present	Absent	Absent	Absent
Bedi *et al.*[2] (2015)	Follicles, nests, chords, plexuses	Present	Present	Present	Present	Present	Absent	Absent	Dentinoid material
Konda *et al.*[12] (2016)	Plexiform	Absent	Absent	Present	Present	Present	Absent	Present	Absent
Kuberappa *et al.*[5] (2020)	Follicle, plexiform	Present	Present	Present	Present	Present	Present	Absent	Absent
Rathore *et al.*[13] (2017)	UAM with mural islands	Present	Present	Present	Present	Present	Present	Absent	Absent

UAM = unicystic ameloblastoma.

side of the mandible, cross the midline and involve the anterior region of the left side.

The lesion was radiologically described as a radiolucency (n = 9, 90%), which was unilocular in two cases and multilocular in seven cases. The radiolucency was well-defined in five cases and ill-defined in three cases. In one case, it was described as an osteolytic lesion with irregular calcifications.[10] The radiological features exhibited by PKA are not pathognomonic and are shared by several other entities. Therefore, odontogenic keratocyst, various benign and malignant odontogenic tumours, benign fibro-osseous lesions and central giant cell granuloma constitute the clinicoradiological differential diagnosis of PKA. The significantly destructive nature of PKA was evident in the radiographs of all the cases, wherein a majority of the cases involved the body, angle and ramus of the mandible (n = 7, 70%). Out of these, two cases exhibited extended involvement up to the sigmoid notch and condylar process.

Additionally, in all the cases that reported findings of computed tomography, buccal and lingual cortical plates exhibited expansion as well as perforation. AM displays a tendency to cause extensive bone destruction and aggressively invades local structures. Increased motility of neoplastic cells due to loss of syndecan-1, besides the increased expression of matrix metalloproteinases (MMPs) and the receptor activator of nuclear factor-kappa B ligand (RANKL), have been suggested as the possible reasons for the aggressive biological nature of AM.[19,20] However, none of the authors have investigated the expression of these markers or genes involved in the reported cases of PKA. Expression of similar markers needs to be studied in cases of PKA to further understand the reasons for its aggressive nature.

Histopathologically, all lesions exhibited an AM component with keratinisation and papilliferous areas. When considering the AM component, the follicular pattern of AM was observed most commonly

(n = 5) [Table 2]. The plexiform pattern of AM was predominant in the case reported by Konda *et al*., which also exhibited areas of desmoplastic changes within the stroma.[12] Two cases exhibited an admixture of the follicular and plexiform pattern.[2,5] In one case, the papilliferous proliferations were present in the primary lumen of a unicystic ameloblastoma (UAM).[13] In the case reported by Collini *et al*., the architecture of tumour cells was described as nests, tubules, islands and even single-file patterns, which simulated the appearance of a salivary gland neoplasm.[10]

Ameloblast-like cells were present in a majority of lesions, wherein low to tall columnar ameloblast-like cells exhibiting nuclear hyperchromatism and reversal of polarity were present in almost all the cases (n = 8, 80%). These cells were present peripherally in the tumour follicles or plexuses. Of these, seven cases exhibited stellate reticulum-like cells, while one case had granular cells towards the centre. Besides ameloblastomatous follicles, some of the follicles were lined by only squamous cells with or without keratin formation.

One case of AM exhibiting papilliferous proliferations reported by Adeyemi *et al*. had basaloid metaplasia within the centre of the follicles.[21] The current study's researchers believe that their case represents a basaloid variant of AM exhibiting papilliferous changes or possibly a hybrid odontogenic tumour. However, since no keratin formation was observed within the tumour islands, the case did not fulfil the criteria for diagnosis of PKA. The earliest cases of PKA reported by Pindborg *et al*. did not exhibit ameloblast-like cells lining the follicles.[4,8] Instead, single to multiple layers of parakeratotic squamous epithelial cells were observed, half of which formed tumour islands while the other half exhibited papilliferous epithelium within a central cystic lumen. Similar parakeratotic-stratified squamous cells were noted in the tumour islands of cases reported by Kuberappa *et al*. and Rathore *et al*., but with the presence of AM-like features in some follicles.[5,13]

A majority of the cases exhibited cystic degeneration centrally within the ameloblastic follicles or plexuses (n = 8, 80%) in which necrotic cell debris was present. It has been suggested that these acantholytic cells separate from the viable epithelial cells in the follicle that continue to proliferate. This differential rate of proliferation and necrosis gives rise to pseudopapillary structures that project into the microcystic lumen.[8] Such phenomena are noted occasionally in AM but are common in odontogenic carcinomas. This suggests a closer histopathological resemblance of PKA to odontogenic neoplasms at the more aggressive end of the spectrum.

PKA has been postulated to be KA in which extensive acantholysis results in pseudopapillary projections.[22] However, true papillae comprising ameloblastoma-like epithelium with a fibrovascular core were also present proliferating in the primary cystic lumen or within the follicles. The centre of tumour follicles, islands, plexuses and nests were packed with stacks of para- or ortho-keratin. In three cases, the stacks of keratin were extruded into the connective tissue stroma and resembled a Pacinian corpuscle-like architecture.[3,9,12]

Classically, AM has been defined as an odontogenic neoplasm of ameloblast-like cells in which the cells do not undergo differentiation to the point of hard tissue formation.[1] Even so, the formation of hard tissues is a frequent finding in KA and was also noted in three cases of PKA. Extruded stacks of keratin have been evidenced to undergo mineralisation, ultimately leading to hard tissue formation. Necrotic tissues may undergo a transition to bone with or without dystrophic calcification—a process termed 'pathologic ossification'. Takeda *et al*. described hard tissue formation to be a result of pathological ossification that produces cellular cementum or woven bone-like material.[9] The transition between keratin accumulation in the stroma to the formation of hard tissue was also evident microscopically in their case. Dystrophic calcifications in the stroma were demonstrated in the case reported by Norval *et al*.[3]

Another entity associated with AM that comprises hard tissue formation is adenoid AM with dentinoid. This dentinoid-producing tumour exhibits characteristic histopathological features of AM and adenomatoid odontogenic tumour (AOT) but is not yet recognised as an official entity by the WHO. The current study's recent literature review discovered 30 cases of Adenoid Ameloblastoma with Dentinoid (AAD) reported to date.[23] Similarly, dentinoid formation could occur in PKA, which was described in one case by Bedi *et al*. Even so, the mechanism of dentinoid formation would be different for AAD (epithelial-mesenchymal induction) and PKA (pathologic ossification), considering the different pathogenesis of both entities. The term 'kerato-odontoameloblastoma' was suggested for such KA with odontogenic hard tissue formation.[2]

While OKC-like features are commonly noted in KA, they were absent in all the cases of PKA.[24] It has been highlighted that OKC may occasionally serve as a source of epithelium for KA development, since it shares a common phenotype and genetic profile with the cells of ameloblastic lineage to some extent.[25] Brannon *et al*. demonstrated the development of mural islands of AM from the lining epithelium of

OKC.[26] Cases exhibiting combined histopathological features have been reported as 'hybrid' lesions by some authors, while others consider them to fall within the spectrum of KA.[24,26] There is a lack of evidence linking OKC with PKA.

Additional histopathological features such as foreign body giant cells, cholesterol clefts, ghost cells, duct-like structures and rosette-like structures were also described across the reported cases of PKA by various authors.[2,5,10] The presence of foreign body giant cells and cholesterol clefts is not surprising; they represent the normal host tissue inflammatory response or constitute a part of the secondary infection of the tumour. The presence of abundant keratin bodies with faint nuclear outlines was implicated as the reason for the resemblance to ghost cells.[5] The follicles with cystic degeneration are occasionally lined by a single layer of epithelium adherent to the basement membrane that imparts a hobnail appearance.[8] A cross-section of such follicles was suggested to be the reason for the apparent duct-like structures.[8,21] The presence of acantholytic cells within such follicles would also impart a rosette-like appearance, leading to the misinterpretation of the lesion as AOT. A highly vascularised stroma was present in the case reported by Kuberappa *et al*. that resembled hemangiomatous AM.[5] Trauma or stimulation of vessels closely associated with the dental follicle has been suggested as the reason for the highly vascular transition of the stroma in AM.[27]

While the tumour cells in a majority of the cases had a benign morphology, a high mitotic rate of 3 mitoses/high power field was reported by Collini *et al*.[10] Recurrences occurred after 39 and 58 months in their case.[10] The patient ultimately succumbed to non-Hodgkin lymphoma (NHL) after six years. They proposed that PKA should be renamed as 'papillary ameloblastic carcinoma', considering its clinically aggressive nature, the microscopic abundance of necrosis and recurrence. Such cases may closely resemble ameloblastic carcinoma, well-differentiated oral squamous cell carcinoma or primary intraosseous carcinoma. Generally, PKA lacks cellular pleomorphism, vascular and neural invasion and abnormal mitoses. The presence of these features can aid in distinguishing PKA from other malignant epithelial or odontogenic neoplasms.

Investigation of the biological chemistry of the tissue using special stains and biomarkers through the employment of IHC has not been extensively studied in cases of PKA. The case reported by Collini *et al*. resembled a salivary gland tumour owing to the presence of tubules and duct-like structures.[10] The authors investigated mucin production utilising Alcian blue, which resulted in negative staining. The salivary gland origin of the tumour was ruled out by negative immunostaining for high-molecular-weight cytokeratins, smooth muscle α-actin, maspin, Glial fibrillary acidic protein and CD45. They found positive immunoexpression of low-molecular-weight cytokeratins in the epithelial cells, vimentin in the stroma and focal and weak expression of S100. Rathore *et al*. highlighted intense immunoexpression of CK19 in the basal and suprabasal layers of the lining epithelium, which was indicative of its odontogenic origin.[28] Ki-67 was intensely expressed in the basal and suprabasal layers, with infrequent positivity in the superficial cells, which was indicative of the high proliferative potential of the cells. They also discovered that p53 was strongly expressed in the basal and suprabasal layers, which is suggestive of mutation in the tumour suppressor gene. The IHC findings of Collini *et al*. and Rathore *et al*. provided further evidence for the aggressive biological potential of the neoplastic odontogenic cells in PKA.[10,13]

Various authors have addressed PKA through different approaches such as wide excision (n = 4, 40%), segmental resection (n = 2, 20%) and hemimandibulectomy (n = 2, 20%). Considering the extensive clinical involvement, presence of atypical cytological features and recurrence, Collini *et al*. performed a modified neck dissection along with the hemimandibulectomy procedure in their case.[10] The lesion recurred 39 months after the treatment procedure, after which no treatment was performed for the recurrent tumour owing to the presence of concomitant NHL. Another recurrence was reported in the study by Bedi *et al*., which occurred three years after an en-bloc resection.[2] The remainder of the cases showed no evidence of disease for a varying follow-up period of two months to one year. However, considering the recurrences in the cases of Collini *et al*. and Bedi *et al*. after three years of treatment, the follow-up period provided by the other authors may not be sufficient to declare a successful outcome.

Except for luminal and intraluminal unicystic ameloblastoma, no difference was observed in the treatment of different variants of AM.[1] Marx and Stern stated that classifying AM according to all the different types of histopathological features would serve to only complicate the classification system, ultimately confusing the clinicians.[29] Even so, the different histopathological types have academic importance and are of interest to pathologists. Therefore, as long as no significant difference is found in the biological behaviour, including different histopathological types of an entity as variants seems the most rational approach. Reports of more cases in future with

extensive long-term follow-up of the outcome would shed more light on the subject of whether PKA is just a variant of AM or a distinct entity. In view of the current evidence, the current study argues that PKA should be considered as a variant of AM within the spectrum of keratinising AMs.

Conclusion

PKA is a rare entity with only 10 reported cases to date—all of which have involved the mandibular posterior region. The clinicodemographic and radiological characteristics of PKA are more similar to those of AM, except that it occurs more commonly in older individuals and shows a marked predilection to occur on the right side. The lesion is locally aggressive, exhibiting extensive clinical involvement of the mandible and adjacent structures. The radiological features of PKA are not pathognomonic and resemble other odontogenic neoplasms. Histopathological presence of papilliferous proliferations of the odontogenic epithelium, besides extensive keratin production that may occur even in the stroma, are characteristics of PKA. Based on the presence of necrotic areas, the high proliferating potential of cells and possible recurrence, the authors recommend that PKA be considered within the spectrum of keratinising AMs towards the more aggressive end. Further studies on biomarkers in PKA, such as syndecan-1, MMPs and RANKL, will aid in elucidating the biological potential of the lesion. With an increasing number of reported cases, more insights could be gained into the possible connections between the pathogenesis of OKC, AA, KA and PKA.

AUTHORS' CONTRIBUTION

SS and TC conceptualised the idea and designed the review. All the authors were responsible for data collection, analysis and resolution of any issues. SS, YA and TC prepared the manuscript, while the content was critically reviewed and edited by MS, AT and RJ. All authors approved the final version of the manuscript.

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