Desmoplastic Ameloblastoma, a Difficult Pathological Entity to Diagnose Pre-Operatively-Review of Literature

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Abstract: Philipsen and Reichart classified ameloblastomas (AM) into 4 subtypes, according to their clinical and biological behavior: intraosseous (solid/multicystic), extraosseous, unicystic, and desmoplastic. Histopathologically, a conventional ameloblastoma subdivided into 6 subtypes, plexiform, follicular, granular cell, acanthomatous, basaloïd and desmoplastic ameloblastoma. According to the literature desmoplastic ameloblastoma (DA) is a rare variant of ameloblastoma. It was first described by Eversole et al., in 1984 as an “ameloblastoma with pronounced desmoplasia” and later on it was further reviewed by Wardlon and El-Mofly et al., in 1987 and by Reichart et al., in 1995. In 2005 the World Health Organization declared DA as a distinct clinic-pathological entity. DA reportedly has a site predilection for the anterior regions of the jaw unlike other Ameloblastomas. Its unique radiographic appearance is that of a mixed radiolucent-radiopaque lesion unlike the strictly radiolucent quality of other ameloblastomas.

In spite of the several scientific literatures, the true biologic profile of DA is still not well understood.

Keywords: ameloblastoma, collision tumor, desmoplastic, intraosseous, osteoplasia.

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I. Introduction

DA predominantly involves the anterior maxilla, quite commonly anterior mandible also, and presents a radiographic appearance that is more typical of a benign fibrousosseous lesion than an Ameloblastoma (AM) [1]. Invasion and continued slow growth are the same in DA as in other ameloblastomas [1-4]. Investigators have observed that recurrence of DA is almost as high as with the conventional ameloblastoma [4, 5]. So, differential diagnosis of DA from benign fibrousosseous lesion or from odontogenic myxoma is far important to prevent its recurrence, and to avoid overtreatment or under-treatment. Radical therapy has been indicated for the treatment of DA [4], which differs to that of resection margins for fibrousosseous lesion or odontogenic myxoma [2, 6].

II. Geographical Distribution

Zhi-Jun Sun et al., reported in a review article of DA, in 2009, that, it is slightly higher in Asian population [7]. The majority of the cases has been reported particularly in Chinese residing in Malaysia and Hong Kong, Malaysians, Japanese and Afro-Caribbeans[8].

Incidence

DA is a rare odontogenic tumor with a reported incidence of only 0.9% to 13% in all AM in different studies [9-12]. In Malaysian population, incidence of DA were 4% of all ameloblastomas and 3% of all odontogenic tumors, as reported by Ng KH et al., in 1993 [11]. In the study among Nigerian population, Effiom et al., (2009) noticed that, out of 330 ameloblastoma cases 5.15% are of DA [13]. But, according to Smullin SE et al., in 2008, incidence of DA, 4% to 13% of all ameloblastomas [14].

III. Types And Nature

DA s have potentially aggressive behaviour [15]. It is classified as intraosseous and peripheral (i.e., no osseous involvement) variants [16]. Intraosseous desmoplastic ameloblastomas may exhibit a more aggressive behaviour [15]. Smullin SE et al., in 2008, reported first case of peripheral variety of DA, involving palate [14]. It has been suggested that the peripheral variety may be an odontogenic hamartomatous lesion and not a true neoplasm- more indolent biologic behaviour [14]. Till 2011 only 2 cases of DA (peripheral variety) were
published in the English literature, reported by Li Bo et al, 2011. They opined that peripheral DAs are similar to conventional peripheral ameloblastomas, as well as exhibiting better biological behaviour [16].

IV. Clinical Features

On first clinical examination, DA represents a non tender swelling (solid mass) with frequent buccal expansion [3, 4, 14, 17–19]. But, there may be a history of pain also [16].

Tooth displacement is common feature for DA (92% of the cases) [20]. Seiji Iida et al, in 2002, reported, that, most cases of the intraoral DA, are mucosa covered bony hard mass, unlike the multicystic ameloblastoma that contains fluid-filled spaces [21].

Peripheral varieties are usually regular in shape, sessile, firm, and small in size. They are known to erode cortical bone by a mass effect that is referred to as “cupping or saucerization”[14].

Age

DA can occur at any age from 13 to 72 years, with a peak in the third (29.1%) and fourth to fifth (41.7%) decades of life. The mean age is 44.1 years [16, 22]. Zhi-Jun-Sun et al, in 2009, reported about two peaks among females, in the 3rd and in the 4th decades, and the males presented only a single peak in the 5th decade. In the fifth decade the incidence rate is a significantly higher in males than females (p < 0.05) [7].

Takata et al, in 1999, reported that the mean age of the patients with DA and non-DA is 40.6 ± 5.9 years and 33.1 ± 2.0 years [12].

Gender

Kaffe et al, (1993), reported that DA more common in females, and the male to female ratio was 1:2 [20]. Bo Li et al, 2011, observed the male-to-female ratio was 55:59 [16]. Philipsen et al, in 2001, observed that DA lesions were equally distributed in both male and female population [4]. In the analysis of DA in Nigerian population by Effiom et al, (2011), it was evident that male to female ratio of 1.27:1 [13]. Takata et al, (1999), of Hiroshima University School of Dentistry, observed, male-to-female ratio was 2.5: 1, during analysis of 89 AM cases, out of which 7 were DA [12].

Site

The DA involves the anterior maxilla predominantly, which is an unusual location for ameloblastoma, but, sometimes ramus is also involved [7, 16]. Philipsen et al, in 2001, reviewed 100 cases of DA, out of which, 51.3% of DA involving maxilla and 48.7% in mandible, in a ratio of maxilla/mandible 1: 0.9 [4].

Michael L. Beckley et al, in 2002, noticed that, the incidence of DA for the maxilla and the mandible is 48% and 52% respectively [22]. A striking difference between DA and Ameloblastoma was found by Kaffe et al, 1993, regarding the anatomic distribution, that DA showed a predilection for the maxilla (73% of the cases) whereas the AM show a marked predilection for the mandible (81% of the cases) [20]. The DA showed a marked predilection for the anterior region of the mandible and maxilla. This region was involved in 73% of the cases; in 40% the lesions were restricted to anterior area of jaw. The molar area was involved in 33% of the cases, but the lesions were never restricted to this area alone, reported by Kaffe et al [20]. Seiji Iida et al, 2002, reported a rare case of DA with significant cystic change in a lesion with extension into the maxillary sinus [21].

Most of the lesions, mentioned in the literature were unilateral, but the midline crossed lesion is also reported by Zhi-Jun Sun et al, in 2009[7].

H.P.H.Philipsen et al, 2001, observed that, out of 76 cases of DA , 15 cases located bilaterally in the incisor canine premolar area(12 in mandible and 3 in maxilla)[4].

Size

Takata et al, in 1999, analysed 7 cases of DA (7.9%) and it was observed, that, the averages of the greatest diameters in mesio-distal and apico-occlusal directions of 7 DAs were 3.6 ± 0.6 cm (range 2.1- 7.0 cm) and 3.0 ± 0.4 cm (range 1.5-4.3 cm), respectively, and those of the non-DA were 5.3 ± 0.3 cm (range 1.5-12.0 cm) and 3.3 ± 0.1 cm (range 0.7-6.0 cm). DA seemed to be smaller in size than non-DA, but there was no statistical significance among the data on tumor size [12]. Retrospective analysis of 115 DA-cases, reported in literature from 1984 to 2008, was done by Zhi-Jun Sun et al, in 2009 and it was observed that 44.4% of the DAs were larger than 3.0 cm, 50.0% smaller than 3.0 cm and only in 5.6% of cases, it was equal to 3.0 cm at the initial presentation [7]. Therefore it may be assumed that DA may be smaller than the “normal” type of ameloblastomas.
V. Radiological Features

Intraosseous lesions of the DAs were classified into 3 types according to radiographic features by Bo Li et al, in 2011,
(1) the osteofibrosis type, most common type, these are unilocular or multilocular destruction with varying amounts of irregular mixed radiolucent/radiopaque materials, similar to that of osteofibrosis lesions.
(2) the radiolucent type of DA (misdiagnosed as a cystic lesion)
(3) the compound type, least common, exhibit mixed radiolucent/radiopaque destruction [16].

Mark et al, supported this observation of Bo Li et al, in Oral Pathology text book [2]. But, according to Iida et al, in 2002, DA may have mixed radiolucent/radiopaque appearance, but, additionally they described “honeycomb” appearance of the DA [21].

P.A. Reichart et al, in 1995, reported that 45% of ameloblastomas with irregular, ill-defined borders were desmoplastic, although this variety is only 2% of all AM [24].

Kaffe et al, reported in 1993, that, well defined borders were present in only 20% of the lesions. In 33% of the lesions, the borders were poorly defined, and in 47% these were diffused, and DA were multilocular in 20% of cases, in 33% it was unilocular and no loculation in 47% of cases [20]. Philipson et al,(1992) opined that presence of osteoplasia due to de novo synthesis of extracellular fibrous protein, which is nidus for calcification and it gives the characteristic mixed radiolucent-radiopaque appearance of DA. According to Philipson et al, radiographically ill-defined borders are suggestive of its infiltrative process with propensity to recur[3].

Kawai et al, in 1999, reported that, DA infiltrates into narrow spaces at the periphery of the tumor. For this mode of tumor growth, adjacent bone trabeculae are prone to persist because osteoblastic activity, which lead to the numerous bony flecks, as seen radiographically, which are attributable to radiographic images of unresorbed or newly formed bony trabeculae [25]. Takata et al, (1999), supported this and they opined that, remnants of non neoplastic bone often seem to remain in tumor tissues and gives unique radiographic features of DA that give an impression of a fibro-osseous lesion due to infiltrative behavior of DA [12]. This benign fibro-osseous like lesion of DA also supported by Eversole et al, 1984[17], Waldron et al, 1987[9] and Kaffe et al, 1993 [20], and Ng KH et al, 1993[11].

But, according to Li Bo et al, DA do not produce bone[16]. The unusual radiographic appearance is attributed to the density of the compressed odontogenic epithelium, which is supported by desmoplastic stroma, and the residual bone, which is invaded by the tumor cells [2]. The pronounced stromal reaction along with local infiltration and non-encapsulation characteristic of DA, is indicative of the defensive response of the host to the “aggressive” tumor [26].

On the basis of these radiographic and histologic findings, it was suggested by Kawai et al, in 1999, that the tumor may develop initially in the periodontal bone, with subsequent growth onto the surface of the original cortex and eventual elevation of the periosteum, resulting in smooth outlined thin cortical margin of the lesion [25]. In DA, tumor islands are usually infiltrated into narrow spaces of surrounding bone [12].

Conic beam computed tomography signs of desmoplastic ameloblastoma, were analysed by Jingjing Luo et al , in 2014[27]. According to them, CBCT has a relatively higher isotropic spatial resolution of osseous structures at lower doses of radiation and lower financial cost than multidetector CT. With clear observation of internal structures in tumors, CBCT can also better distinguish DA from fibro-osseous lesions compared with panoramic radiography. DA lesions with mixed radiolucent/radiopaque content were variously described as “granular or cloudy,” “needle-like trabecular,” “highly dense trabecular,” or having “honeycomb appearance.” The honeycomb-like appearance of DA in CBCT is formed by coarse trabecular septa. In CBCT of DA, radiopaque flecks scattered around the radiolucent region are more common than other intraosseous ameloblastoma. Another characteristic CBCT feature of DA that the apparent expansion of a lesion in the labial/buccal side with partial cortical erosion, whereas other common intraosseous ameloblastoma lesions often exhibit buccolingual expansion with perforation[27].

Kaffe et al, observed root resorption in 33% of the cases [20]. But, Li et al, in 2011, reported, root resorption 8.7% of patients (2 of 23). Root displacement was involved in 47.9% of patients (11 of 23) [16]. Both buccal and lingual/palatal cortical plate expansion were evident in literatures [14, 17, 4, 10, 12, 18].

VI. Relation With Impacted Tooth

Although 48% of the non-DA were associated with embedded teeth (exclusively mandibular third molars), there was no such association with DA, narrated by Takata et al, (1999) [12].

VII. Histopathological Study

There are two histologic variants of DA, simple DA (predominant in 88.0%) and DA with osteoplasia ( rare, in 12.0%) [13, 28].
Eversole et al, first described DA as a lesion with unique histologic pattern characterized by presence of islands of ameloblastic columnar cells surrounding spindle-shapedstellate reticulum–like cells in a stroma with marked desmoplasia [17]. Extensive a hypocellular [14] stromal desmoplasia is striking and constant finding , characterised by moderate cellular fibrous connective tissue with abundant thick collagen fibres , that seems to compress "squeeze" the odontogenic epithelial island from the periphery[4]. This pronounced stromal reaction characteristic of DAs can be viewed as a defensive response of the host to the "aggressive" tumor [11,12]. Lesion is surrounded by peripheral fibrous condensation, reported by Takata et al [12], also supported by Gardner DG et al [29], Seiji Iida et al [21] and Ng KH[11].

Philipsen et al, in 1992, narrated that, when the desmoplasia is caused by stimulation of stromal fibroblast within tumor cell, it also affects another type of mesenchymal cell, namely, the osteoblast, and produce new bone (osteoplasia) [3]. This metaplastic bony trabeculae (osteoplasia) rimmed by active osteoblast also noticed by Philipsen et al, in 2001[4] and Savithri V et al, in 2013 [30].

For this mode of tumor growth, adjacent bone trabeculae are prone to persist because osteoblastic activity, rather more vigorous than osteoclastic activity, may be induced by these neoplastic cells [25].

There is another histological variety, "Hybrid" lesion of ameloblastoma (HLA)/collision tumor, first described by Waldron and El-Mofly, where follicular or plexiform solid multicystic ameloblastoma (SMA) coexist with areas characteristic of DAs [30]. Hirota et al, described a case of “hybrid” lesions of ameloblastoma in 2005 [18].

VIII. Immunohistochemistry

In a comparative immunohistochemical study, connective tissue stroma of a DA exhibits a strong positive reaction for collagen type VI, which is indicator of active de novo synthesis of extracellular matrix protein in contrary to that of solid multicystic ameloblastoma(follicular ameloblastoma) [3,31]. In contrary to solid multicystic ameloblastoma, there was marked expression of transforming growth factor (TGF-β) in most DA cases. It was suggested by Philipsen et al, in a book , named Odontogenic Tumors and Allied lesions, that , TGF-β produced by tumor cells of DA plays a part in the prominent desmoplastic matrix formation[31].

IX. Malignant Potentiality

Yoshimura et al, in 1990, reported that there were no malignant form of DA, evident in the literature [32].

X. Differential Diagnosis

DA (type II) is usually similar in appearance to cyst like radiolucency and is frequently clinically misdiagnosed as an odontogenic cyst, including radicular cyst and globulomaxillary cyst [9, 16, 33].

Tumors that are characteristically radiolucent-radioopaque should be differentiated from fibro-osseous lesion (like ossifying fibromas, fibrous dysplasia), osteoblastomas, osteosarcomas, calcifying epithelial odontogenic tumors, and calcifying odontogenic cysts, chronic osteomyelitis [2, 7, 21]. Desmoplastic ameloblastoma with scattered radiopacities with in the radiolucent lesion give an impression of non-ameloblastomatous lesions such as odontogenic myxoma and even osteosarcoma , reported by Takata et al, 1999 [12].

The appearance of fibrous dysplasia on plain radiographs depends on the age of the patient, the chronicity of the lesion, and the activity of the tumor. In quiescent and nonaggressive lesions, the bone is enlarged or expanded and the matrix may be densely radioopaque or may have a “ground glass” appearance. The more mature the lesion, the more radiodense it appears on plain radiographs. In patients with aggressive lesions, the bony contour is expanded and there is often cortical thinning, cortical perforation, displaced teeth, and root resorption. Fibrous dysplasia of the jaws are often poorly defined, whereas in the long bones they are circumscribed with a sclerotic periphery. In the mandible, Fibrous dysplasia frequently arises below the inferior alveolar canal and displaces it superiorly[34]. The “hypercellular” pattern of Fibrous dysplasia is observed in the jaws and is characterized by dense, ordered, and often parallel bone trabeculae. Osteoblasts and osteoclasts are scant within the lesions[34]. But, en block resection for complete excision of fibrous dysplasia lesion is impractical and unnecessary, as mentioned in text book of surgical pathology, by Fonseca [6]. For, fibrousosseous lesion preservation of adjacent normal structure, like teeth, neurovascular bundle etc. is preferred[6].

An intraosseous salivary gland tumor sometimes should be considered as differential diagnosis of DA. Because in DA, there is cystic degeneration of tumor islands and pseudocyst formation, which seem to be features of gland tumors [18].

Odontogenic myxoma should be differentiated from DA. Radiologically, odontogenic myxoma may have a ‘soap bubble’ or ‘honeycomb’ appearance [2, 6]. Tooth displacement and root resorption may be seen, as might displacement of the inferior alveolar canal, which is indicative of its benign process [2]. Odontogenic myxomas are unencapsulated, infiltrating, gelatinous tumors that are sparsely cellular. The cells are spindle shaped or stellate with long cytoplasmic processes[2]. Curative treatment of an odontogenic myxoma is
accomplished by resection with 1.0- to 1.5-cm bony margins and one uninvolved anatomical barrier margin[2]. For odontogenic myxoma neurovascular bundle of the mandible should not be sacrificed routinely, even in resection with continuity defect. Only if the bundle is hopelessly involved by tumor, it should be included in the resection. If the bundle is displaced rather than incorporated, and if separable from the tumor, it can be preserved [6].

XI. Treatment Protocol

Marx et al, opined in the text book of Oral pathology, that DA should be treated with same to that of SMA [2]. Sun et al, 2009, opined that, more radical approach is required for the ill-defined borders of DA [7]. This non-encapsulated tumor invariably infiltrates between trabeculae of the cancellous bone (masking beneath a normal looking cortical bone), which leads its high propensity to recur. So, curettage is never an appropriate treatment for DA. Wide margin surgical extirpation is the mainstay of treatment, opined by Yoshimura et al, in 2009 [32].

Soft tissue removal is advocated when cortical perforation or soft tissue infiltration is evident. Therefore, removal of adjacent soft tissue extending to the next adjacent anatomic boundary must be performed. Reconstruction of the neo-mandible should encompass the scope of restoration of speech, mastication and facial contour [35].

Maxillary involvement can potentially lead to more devastating outcomes if not treated promptly, and its radiographic appearance may lead clinicians to misdiagnose the swelling as a benign fibroosseous lesion, opined by Suvy Manuel et al, in 2002 [36]. Yoshimura and Saito, in 1990, reported a case of desmoplastic ameloblastoma of the anterior maxilla, which was treated with subtotal maxillectomy [32], with 1.5 cm tumor margins, as reported in the literature[36]. According to text book of Fonseca, a safe margin for resection of uninvolved bone is approximately 2 cm for solid multicystic ameloblastoma. And, if the IAN(inferior alveolar nerve) lies within the lesion for SMA, it should be sacrificed[6].

The peripheral ameloblastoma is typically treated by local soft tissue excision to achieve 2- to 3-mm margins. Recurrence is rare and is more likely the result of incomplete excision rather than aggressiveness of the tumor, stated by Smullin SE et al, in 2008 [14].

XII. Incidence Of Recurrence

The tendency toward local recurrence after conservative surgical treatment is evident in the literature[16]. Investigators have observed that recurrence rate of DA (15.9%) is almost as high as with the conventional ameloblastoma [7, 9, 23]. Keszler et al, 1996, even reported a higher recurrence rate (21.4%) than the other type (10.1%) of ameloblastoma [23].

As per Takashi et al, 1999, recurrence rate was 14% in DA and 20% in non-DA. All the cases with Recurrences were evident in both DA or non-DA, where the cases were treated with curettage and/or marsupialization, while there was no recurrence in cases treated by resection [12].This statement was also supported by Beckley M.L et al, 2002 [22], Yuko Itoh et al, 2012 [28].

FIGURES

![Panoramic radiograph showing mixed radiolucent radio-opacity with ill-defined borders(DA).](image-url)
Desmoplastic ameloblastoma, a difficult pathological entity to diagnose pre-operatively—Review of

Figure 2: Panoramic radiograph showing honeycomb appearance (DA).

Figure 3: Axial CT scan (bony window) showing characteristic “honeycomb” appearance of DA involving left side of mandible

XIII. Conclusion

DA is a rare variety of ameloblastoma in every aspect and its treatment protocol varies greatly than those lesions simulating DA. But, it is difficult to diagnose for its atypical presentation both clinically and radiologically. It is aggressive by nature, so early diagnosis is the most important part for its proper treatment.

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