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Histopathological Heterogeneity in Hybrid Ameloblastoma: A Case Report

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Abstract: ***Ameloblastoma is one of the most common odontogenic tumors of epithelial origin, exhibiting several histological subtypes. Among these, hybrid ameloblastoma is a rare entity characterized by the coexistence of multiple histopathological patterns within the same lesion. Here we report a case of hybrid ameloblastoma in a 51-year-old female patient involving the right side of the mandible. Radiographic evaluation revealed a mixed radiolucent-radiopaque multilocular lesion. The incisional biopsy suggested desmoplastic ameloblastoma, whereas the excisional biopsy revealed a broader histopathological spectrum, comprising desmoplastic, follicular, plexiform, and acanthomatous patterns. The treatment of choice was segmental resection of the tumor. This case highlights the diagnostic challenge and biological heterogeneity associated with hybrid ameloblastoma. Recognition of its diverse histopathological features is crucial for accurate diagnosis and appropriate surgical management.***

Keywords: Hybrid ameloblastoma, Benign odontogenic tumor, Histopathological Heterogeneity

1.Introduction

Ameloblastoma is the most common clinically significant odontogenic tumor, originating from odontogenic epithelium. It may develop from remnants of the dental lamina, the enamel organ, the epithelial lining of an odontogenic cyst, or basal cells of the oral mucosa. Ameloblastomas are slow-growing, locally invasive tumors that run a benign course in most cases[1]. They most commonly occur between the third and fifth decades of life and show no significant gender predilection. Approximately 80% of cases arise in the mandible, predominantly in the ramus and body regions, while only 20% are found in the maxilla[2]. The tumor is often asymptomatic, and smaller lesions are detected only during a radiographic examination. A painless swelling or expansion of the jaw is the usual clinical presentation. The most typical radiographic feature is that of a multilocular radiolucent lesion. The lesion is often described as having a "soap bubble" appearance (when the radiolucent loculations are large) or as being "honeycombed" (when the loculations are small)[3]

According to the 5th edition of the "World Health Organization (WHO) Classification of Head and Neck Tumours" ameloblastoma is categorizes into 5 types- unicystic, extraosseous, conventional, Adenoid ameloblastoma, Metastasizing ameloblastoma[4]. *Unicystic Ameloblastoma* has three subtypes according to the distribution of the proliferating ameloblastomatous epithelium: luminal, intraluminal and mural. Several microscopic subtypes of conventional ameloblastoma have been recognized like follicular, plexiform, acanthomatous, granular cell, desmoplastic, and basal cell types. Adenoid ameloblastoma (AA) is the newly recognized entity among odontogenic lesions. It is defined as an epithelial odontogenic neoplasm characterized by a cribriform architecture, duct-like structures, and often associated with the presence of dentinoid material[5]. The BRAFp.V600E mutation is the most common activating mutation in ameloblastoma, impacting the MAPK pathway and representing an early and crucial event in its etiopathogenesis. The molecular and genetic transformation of odontogenic epithelium into ameloblastoma is strongly associated with dysregulation of key signaling pathways, including MAPK, Sonic Hedgehog, and WNT/β-catenin[6].

In 1987, Waldron and El-Mofty coined a novel variant of ameloblastoma termed hybrid ameloblastoma, which exhibits an unpredictable combination of histopathological features from both desmoplastic and conventional ameloblastoma[7]. Hybrid ameloblastoma shows a mixture of histological patterns, most commonly combining follicular and plexiform types, along with features of other variants such as desmoplastic and acanthomatous forms. This histological heterogeneity pose challenges in diagnosis and treatment planning. The present case report highlights a rare occurrence of an ameloblastoma that histologically exhibits a combination of ameloblastic follicles, plexiform patterns, acanthomatous changes, and a desmoplastic component, underscoring the uncommon nature of such lesions.

2.Case Report

A 51-year-old female reported to the Department of Oral Pathology & Microbiology, with the complaint of painless swelling in the right side of lower jaw which had been present from 2 months. The swelling began spontaneously and gradually increased in size and without causing any pain. The patient did not report any history of trauma to the affected area and had no contributory past medical history.

Clinical examination revealed no abnormal findings in general physical or extra oral examination. There were no gross facial asymmetry and no abnormality on the visible skin surfaces. However, upon palpation, a slight bony hard

bulge was felt in the right body of mandible. Intra oral examination revealed a single rounded swelling on the buccal aspect of 42-44 approximately 2 cm × 2 cm in size. The swelling was firm to hard in consistency and obliterated the buccal sulcus though the overlying mucosa appeared normal [Figure 1].

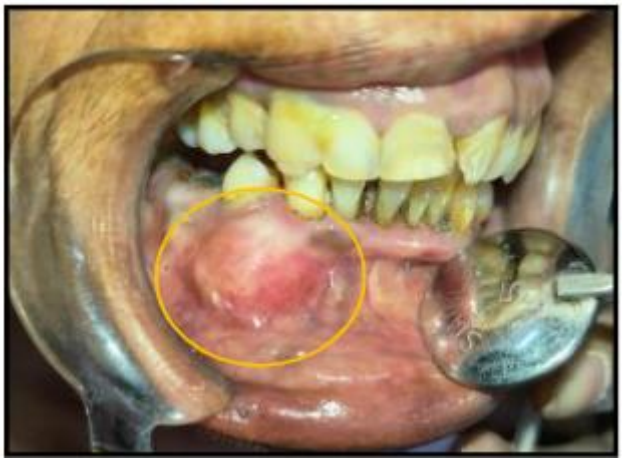

Figure 1: Intraoral examination showing buccal cortical plate

A panoramic radiograph revealed a mixed radiolucent–radiopaque, multilocular lesion with a irregular sclerotic border. The lesion extended anteroposteriorly from the mesial aspect of tooth 42 to the mesial aspect of tooth 44, and superoinferiorly from the upper border of the mandible to approximately 2 cm above the lower border [Figure 2]. Root pieces of 44,45 and 46 were visible within the lesion. Computed tomography demonstrated a multiloculated, expansile, well-demarcated lytic lesion in the right mandibular body, involving the alveolar process in the region of the lateral incisor, canine, and first premolar [Figure 3]

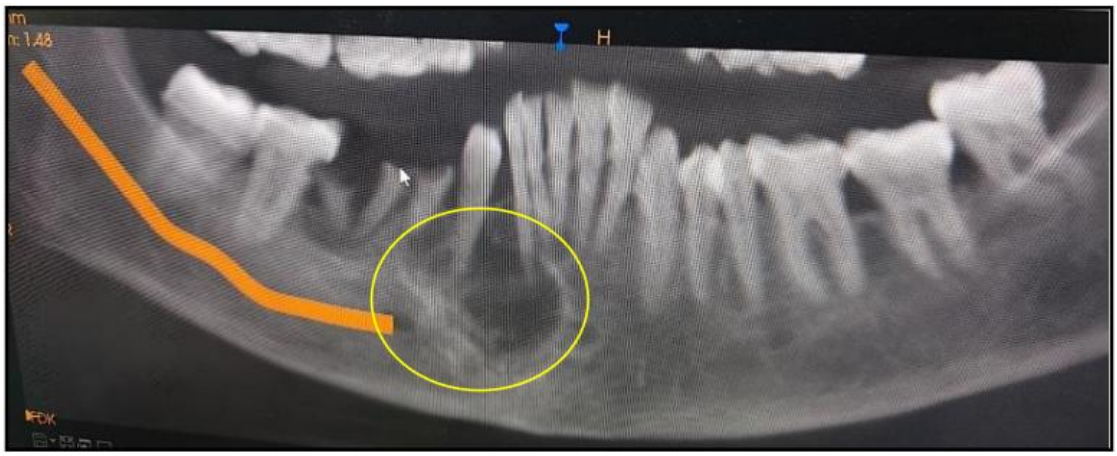

Figure 2: OPG showing mixed radiolucent–radiopaque multilocular lesion wrt to apex of 42-44

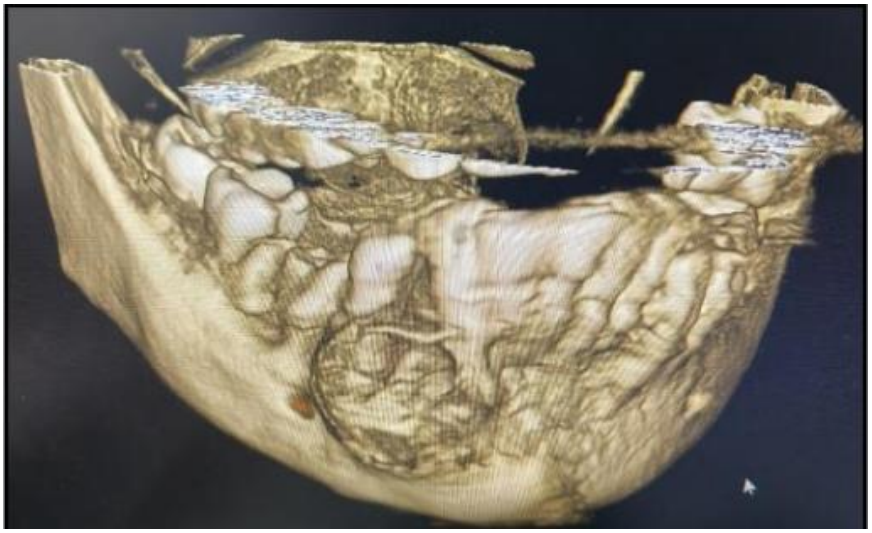

Figure 3: 3d computed tomography shows multiloculated, well demarcated lesion in right mandibular body

An incisional biopsy was performed by reflecting mucoperiosteal flap. Gross examination of the lesional tissue revealed specimens of variable size, firm to hard in consistency, and whitish-brown in color [Figure 4].

Figure 4: Gross examination of incisional biopsy

Histopathological examination of Hematoxylin & Eosin stained sections of multiple soft tissue specimens exhibit odontogenic island arranged in various configuration. These odontogenic islands were predominantly in kite shaped showing tall columnar cells with hyperchromatic nuclei and central stellate reticulum like cells. The connective tissue stroma showed hyalinization with dense collagen fibre bundles along with fibroblasts and fibrocytes. Focal calcifications were evident at periphery and mild degree of chronic inflammatory cell infiltrate and vascularity was present. The deeper section demonstrated osseous trabeculae. Overall features were suggestive of Desmoplastic Ameloblastoma.

For the excisional biopsy, a segmental resection was performed. The surgical specimen consists of multiple tissue fragments and extracted teeth. The largest fragment measured 4×***3.5***cm, comprising a portion of alveolar bone with attached teeth. The overlying soft tissue appeared whitish to pale brown, firm in consistency, with irregular surface. One fragment consists predominantly of whitish soft tissue, firm in consistency [Figure 5].

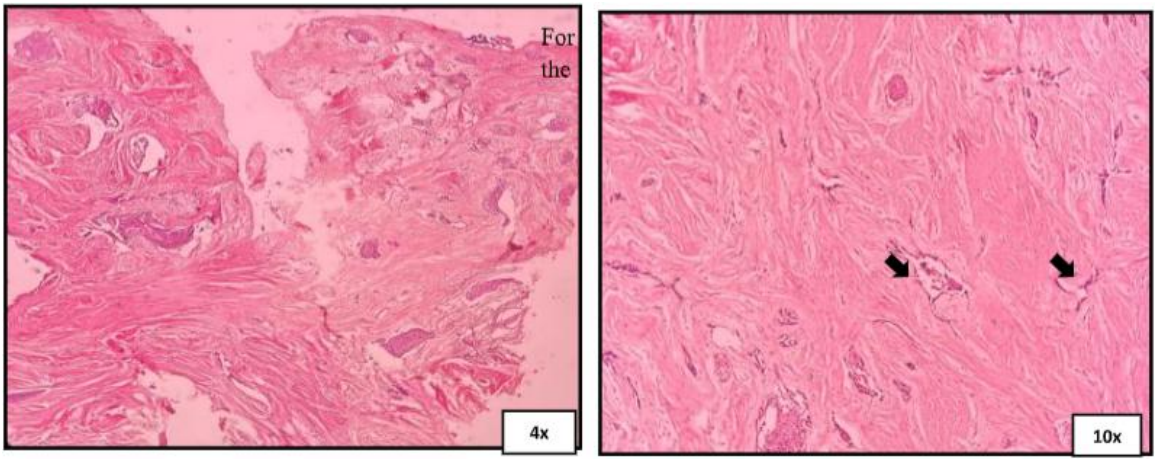

Figure 5: Odontogenic islands arranged in kite shape with hyalinized connective tissue stroma

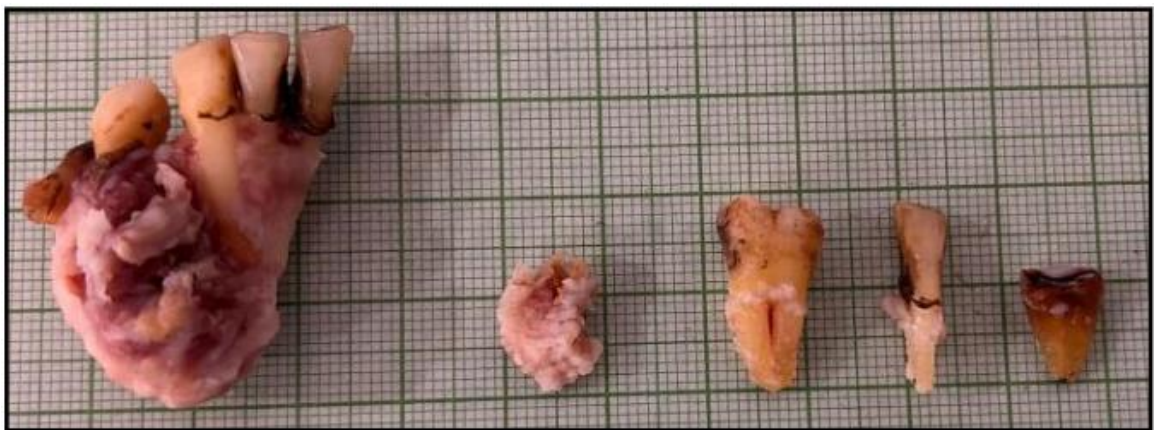

Figure 6: Gross examination of excisional biopsy

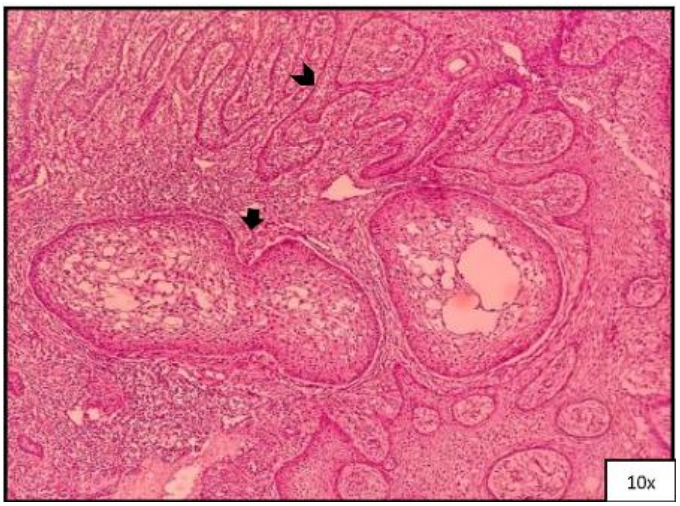

Figure 7: H/E stained sections shows odontogenic epithelium arranged in follicle, strands, cords and nests configuration. Ameloblastic follicular(arrow) and plexiform pattern(arrowhead)

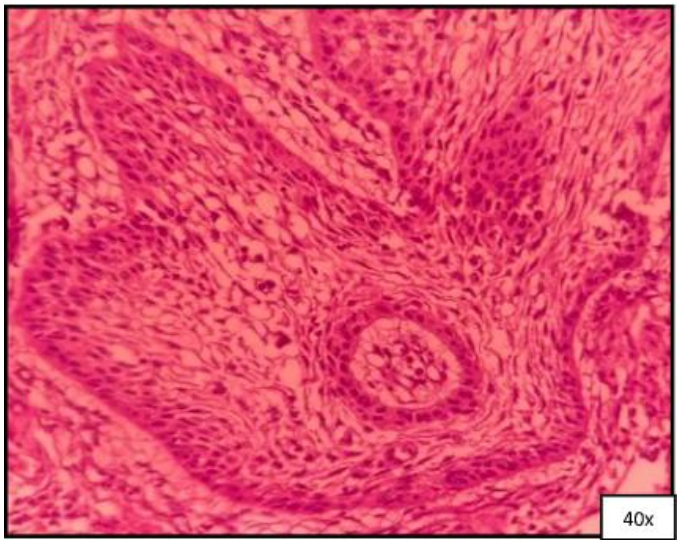

Figure 8: Ameloblastic follicle showing peripheral columnar cells with palisading appearance and reversal of polarity and central loosely arranged cells resembling stellate reticulum like cells.

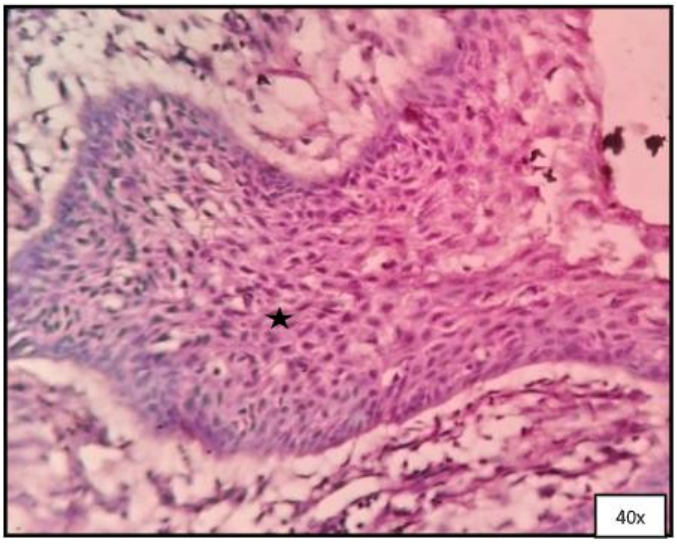

Figure 9: Ameloblastic follicle showing peripheral cells with cuboidal to columnar in shape and squamous metaplasia (star) indicating acanthomatous changes

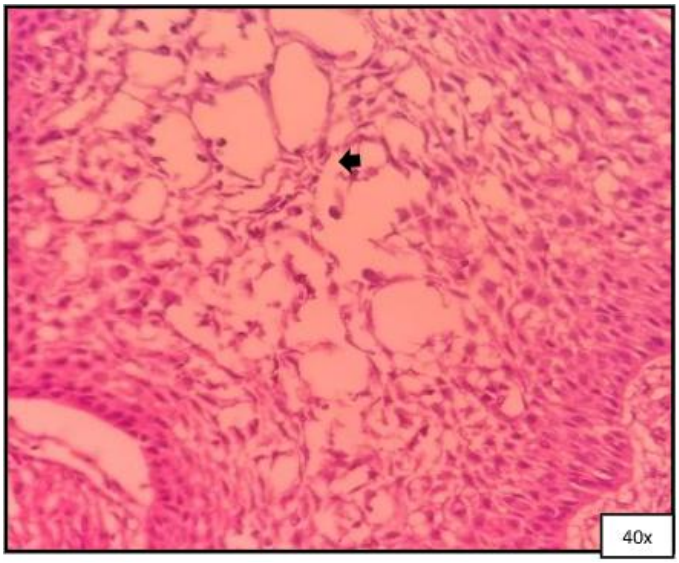

Figure 10: Ameloblastic follicle showing cystic

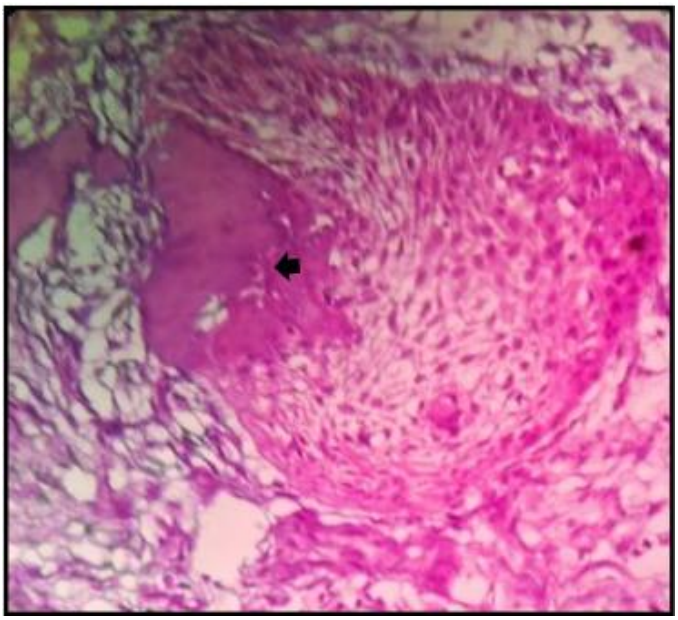

Figure 11: Ameloblastic follicle showing osteoplasia

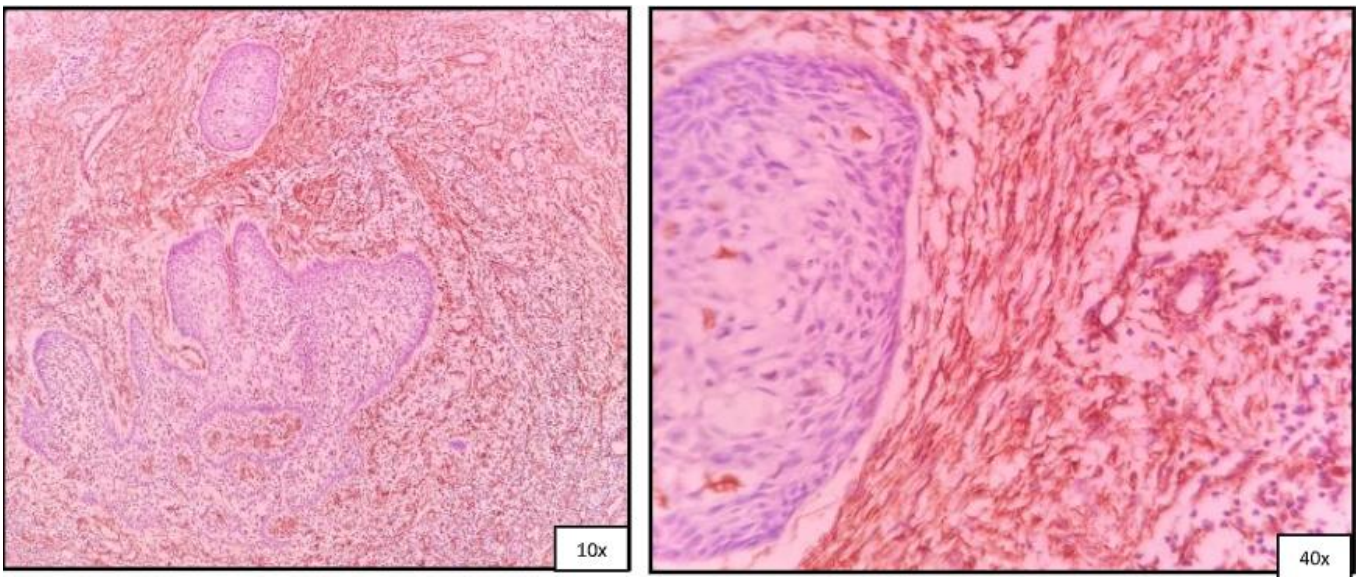

Figure 12: Collagen VI is strongly positive in connective tissue stroma

Histopathological examination of H/E stained sections from lesional tissue revealed odontogenic epithelium arranged in follicle, strands, cords and nests. The odontogenic follicle were lined by columnar cells in palisading arrangement showing reversal of polarity and loosely arranged central stellate reticulum like cells. Few islands showed acanthomatous changes, cystic degeneration and areas of osteoplasia. The connective tissue stroma was hyalinized with dense collagen fibres, fibroblasts and fibrocytes. A severe degree of chronic inflammatory cell infiltrate chiefly lymphocytes and plasma cells was observed, along with moderate to severe degree of vascularity with dilated blood vessels. The deeper section showed osseous trabeculae and muscle fibre bundles. The immunohistochemical analysis revealed strong positive expression of Collagen VI adjacent to tumor islands. The final histopathological diagnosis was consistent with Hybrid Ameloblastoma.

3.Discussion

Ameloblastoma is a conventional odontogenic neoplasm that accounts for approximately 18% of all odontogenic jaw tumors. Among its histological subtypes, the follicular (32.5%) and plexiform (28.2%) patterns are the most common, whereas the desmoplastic variant is relatively rare, with an incidence ranging between 4% and 13%[8]. Hybrid lesions are characterized by the presence of two or more distinct histopathological patterns, with each retaining the typical features associated with different entities. According to Waldron and El-Mofty, hybrid ameloblastoma is a rare variant characterized by a distinctive combination of the histological features of desmoplastic ameloblastoma and conventional ameloblastoma[9]. This unique histological presentation is thought to reflect the diverse differentiation potential of odontogenic epithelial cells. In hybrid lesions, areas of solid ameloblastoma usually display plexiform and follicular patterns. Rarely, these solid areas show basal cell, granular cell, or squamous metaplasia or acanthomatous patterns[10].

Hybrid ameloblastoma shows a high predilection for posterior mandible as observed in the present case. Radiographically, it often mimics fibro-osseous lesions and various odontogenic cysts and tumors, typically presenting with a mixed radiolucent–radiopaque internal structure due to osseous metaplasia within the dense fibrous septa. The radiological differential diagnosis includes ossifying fibroma, fibrous dysplasia, osteoblastoma, osteosarcoma, calcifying epithelial odontogenic tumor, and calcifying odontogenic cyst[10,11]. In present case, the tumor was located in the mandibular anterior region extending posteriorly towards the premolar region and displayed follicular, plexiform, acanthomatous, and desmoplastic components.

The origin of hybrid ameloblastoma remains a topic of debate. Waldron and El-Mofty (1987) proposed two possible mechanisms: (i) a secondary desmoplastic transformation occurring within the stroma of a conventional ameloblastoma, or (ii) areas of a primary desmoplastic ameloblastoma undergoing transition into a conventional pattern. Both processes may result in a lesion displaying a mosaic of desmoplastic and conventional features (10). In contrast, Philipsen et al. suggested that hybrid ameloblastoma may represent an intermediate or transitional variant of desmoplastic ameloblastoma, displaying microscopic characteristics of both subtypes. Some investigators have described hybrid ameloblastoma as a potential collision tumor, arising from the simultaneous presence of desmoplastic and conventional ameloblastoma components within the same lesion.[12.13]

On incisional biopsy, the lesion demonstrated the classical histopathological features of desmoplastic ameloblastoma (DA). The most striking feature was marked stromal desmoplasia, consisting of moderately cellular fibrous connective tissue with abundance of densely packed collagen fibers. This excessive stromal reaction exerted compressive forces on the odontogenic epithelial islands and cords, imparting a characteristic pointed, stellate, or “kite-like” morphology[10,12]. The desmoplastic reaction, believed to be initiated by stromal cells through the production of collagen and extracellular matrix proteins, may also facilitate tumor cell migration and local invasion, as has been proposed in other neoplasms[14].

In contrast, the excisional biopsy revealed a broader histopathological spectrum. The odontogenic epithelium was arranged in follicular, cord-like, strand-like, and nest-like patterns. Several areas exhibited well-formed odontogenic follicles lined peripherally by ameloblast-like columnar or cuboidal cells demonstrating palisading and nuclear polarization. The central regions of these follicles resembled stellate reticulum-like cells, with focal evidence of squamous metaplasia and cystic degeneration[1]. Other areas showed compressed odontogenic epithelial islands, where the peripheral cells appeared cuboidal and the central portion contained indistinct or inconspicuous cells, likely reflecting the pressure exerted by the desmoplastic stroma[15]. A noteworthy additional finding was osteoplasia, characterized by the presence of metaplastic woven as well as mature lamellar bony trabeculae. These trabeculae frequently contained entrapped osteocytes and were lined by plump, active osteoblasts, indicating ongoing bone formation. The osteogenic activity may be attributed to tumor–stromal interactions, wherein neoplastic odontogenic cells stimulate osteoblast differentiation and new bone deposition[16,17]. Collectively, these histopathological observations underscore the hybrid nature of the lesion, with areas displaying the desmoplastic features alongside regions resembling the conventional type, thereby highlighting the biological heterogeneity of ameloblastoma.

Immunohistochemical analysis revealed that the stroma of desmoplastic ameloblastoma demonstrates strong immunoreactivity for collagen type VI, reflecting an active de novo synthesis of extracellular matrix proteins rather than a mere reparative or scar-related process. The intense expression of collagen type VI is considered a distinctive feature, serving to differentiate desmoplastic ameloblastoma from other histological subtypes of ameloblastoma.

Given currently limited understanding of the biological behavior and prognosis of hybrid ameloblastoma, optimal treatment strategies remain to be fully established. Based on the presently available evidence. The World Health Organization (WHO) recommends managing these lesions in the same manner as conventional solid/multicystic ameloblastoma, which involves complete surgical resection. This approach is advised because more conservative methods, such as enucleation or curettage, are associated with a higher risk of recurrence. Nevertheless, small, well-circumscribed lesions may be amenable to complete enucleation in toto.

4.Conclusion

Hybrid ameloblastoma represents a rare histopathological variant characterized by the coexistence of conventional and desmoplastic features within a single lesion. Its biological behaviour is not yet fully understood, but available evidence suggests that it shares the locally aggressive nature of solid/multicystic ameloblastoma. The presence of desmoplastic stroma, compressed odontogenic islands, and areas exhibiting conventional follicular or plexiform patterns highlight its histological heterogeneity. Given the potential for recurrence, particularly following conservative management, complete surgical resection with adequate margins remains the preferred approach of treatment. Furthermore, long-term follow-up is essential, as the unpredictable nature of hybrid lesions warrants careful monitoring to better understand their prognosis and therapeutic implications.

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