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Case report

Carcinoma ex-pleomorphic adenoma of mandible: A case report and review of literature

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ABSTRACT

Introduction and importance: The most common benign neoplasm of major and minor salivary glands is pleomorphic adenoma (PA). Around 80 % of all parotid neoplasms are pleomorphic adenomas, while 44–68 % and 38–43 % tumors were pleomorphic adenomas of submandibular and minor salivary gland tumors. PA has been reported in a variety of anatomic locations including true intraosseous mandibular tumor, external ear canal, TMJ region, lacrimal gland, epiglottis, larynx and nasopharynx, breast, lung, esophagus, sinonasal and skull base and trachea.

Pleomorphic adenoma has a tendency to transform into a number of malignancies; carcinoma ex-pleomorphic adenoma, carcinosarcoma or metastasizing pleomorphic adenoma. Pleomorphic adenomas most commonly transform into carcinoma ex-pleomorphic adenoma (CEPA).

Case presentation: A 30-year-old male presented with the primary complaint of a long-standing swelling at his right mandibular region for past 18 months. On intra oral examination, there was a non-healing alveolar socket of right lower 3rd molar tooth while rest of the dentition and mucosal surfaces were normal. On extra oral examination, mouth opening was adequate with intact lower border of the mandible and no palpable lymph nodes in the neck. Initial biopsy of lesion showed pleomorphic adenoma, but later the lesion came out to be carcinoma ex-pleomorphic adenoma, for which he underwent segmental mandibulectomy and free fibular flap.

Clinical discussion: The prevalence of CEPA transformation from pleomorphic adenoma is 1.5 % within the first 5 years of diagnosis, going up to 10 % after 15 years. The true rate of malignant transformation in recurrent pleomorphic adenoma is reported to be 3.3 %. We report a case of an intra-osseous carcinoma ex pleomorphic adenoma (CEPA) of the mandible. It is thought that ectopic entrapment of salivary tissue or developmentally included embryonic remnants of submandibular glands within recesses or lacunae of the mandibular bone could explain the intraosseous origin of a salivary gland tumor in the mandible. Since carcinoma ex pleomorphic adenoma (CEPA) arises from primary or recurrent pleomorphic adenoma, therefore it poses a diagnostic challenge for histopathologists. The radiographic picture of primary tumor/recurrence can mimic odontogenic cyst/tumor; therefore, a sinister disease process should always be kept in mind. In the post operative period, regular follow up is required to treat any recurrence. The recurrence rate for such disease has not been documented.

Conclusion: Intra osseous CEPA is a very rare tumor. Intra bony tumors which rapidly increase in size have signs and symptoms of nerve involvement and cause bony destruction should have a high suspicion of index of malignancy. Therefore, biopsy must be correlated with clinical and radiological features. Regular follow up is necessary to detect any recurrence promptly.

1. Introduction

The most common benign neoplasm of major and minor salivary glands is pleomorphic adenoma (PA). Around 80 % of all parotid neoplasms are pleomorphic adenomas [1–3], while 44–68 % and 38–43 % tumors were pleomorphic adenomas of submandibular and minor

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salivary gland tumors [4]. The mean age of presentation of the PA is 30–50 years with a predilection for females [5]. Classically, PA is a well encapsulated tumor which contains epithelial and myoepithelial cells. PA has been reported in a variety of anatomic locations including true intraosseous mandibular tumor, external ear canal, TMJ region, lacrimal gland, epiglottis, larynx and nasopharynx, breast, lung, esophagus, sinonasal and skull base and trachea [6].

Pleomorphic adenoma has a tendency to transform into a number of malignancies; carcinoma ex-pleomorphic adenoma, carcinosarcoma or metastasizing pleomorphic adenoma. Pleomorphic adenomas most commonly transform into carcinoma ex-pleomorphic adenoma (CEPA) [7]. The overall incidence of carcinoma ex-pleomorphic adenoma in the literature is 3.6 % among all salivary gland tumors and 11.6 % among all the malignant neoplasms of salivary glands [8]. The pathogenesis of CEPA is uncertain, it could be a malignant transformation of benign pleomorphic adenoma or could be a malignant entity from the onset [9]. Histopathologically, it has been divided into 3 categories, i.e., intracapsular, minimally invasive and widely invasive carcinomas. Since CEPA is an aggressive carcinoma, it is important to detect it as early as possible. It is believed that not more than half of the total CEPA cases are detected before surgical intervention [10]. This late detection means that many CEPA go undiagnosed on initial cytological exam and hence increased morbidity or even mortality of the patient [11]. We report a case of intra osseous CEPA of the mandible.

The work has been reported in line with the SCARE criteria [23].

2. Case report

A 30-year-old male presented to the head and neck surgery clinic with the primary complaint of a long-standing swelling at his right mandibular region for past 18 months. His medical history was not significant for any disease, previous surgery and family or personal history of any malignancy. He had a three years history of cigarette smoking. The patient reported discomfort from cheek biting. He visited his local oral surgeon who extracted right upper and lower third molar. In the post operative period, the wound of his right lower third molar did not heal. He presented to head and neck clinic with mild facial swelling in the region of right angle of mandible. On intra oral examination, there was a non-healing alveolar socket of right lower 3rd molar tooth while rest of the dentition and mucosal surfaces were normal. There was no paresthesia of the inferior alveolar nerve. On extra oral examination, mouth opening was adequate with intact lower border of the mandible and no palpable lymph nodes in the neck. On orthopantomogram (Fig. 1), a large radiolucent lesion was seen on the right side of the mandible starting from the right lower 2nd molar to the ramus of the mandible on the same side. No fracture was noted on the OPG.

Other risk factors included a smoking history of 3 years. Next, imaging was advised and the CT scan showed a large expansile destructive lesion measuring 4.7 × 3.4 × 8 cm involving the right mandible with its epicenter at the angle (Fig. 2). The CT scan also showed extension of the tumor into the ramus, coronoid and condylar processes with areas of cortical perforation.

The CT findings were suggestive of a locally aggressive tumor with differentials including an aggressive ameloblastoma or a malignant primary osseous neoplasm like sarcoma. An incisional biopsy performed and reported outside was suggestive of pleomorphic adenoma. Since the previous biopsy was done outside a year ago and looking at the aggressive clinical and radiological picture of the lesion, it was decided to perform an examination under anesthesia (EUA) and re-biopsy the lesion. All complications especially the potential for pathological/iatrogenic fracture of the mandibular bone was also discussed with the patient. On histological examination, biopsy of the intraosseous lesion revealed the diagnosis of carcinoma ex pleomorphic adenoma (CEPA). The case was discussed in a multidisciplinary team meeting (MDT), a segmental mandibulectomy and disarticulation with ipsilateral neck dissection and fibula free flap reconstruction (FFFR) was offered to the patient.

Intraoperatively, intra osseous tumor was visualized along with cortical perforation and expansion of ramus and angle of the mandible noted up to level of the lower right second molar tooth. The tumor was excised and removed intact with the surrounding overlying muscles (Fig. 3). Ipsilateral neck dissection level 1–3 was performed with standard technique. Final histopathology of the lesion showed carcinoma ex pleomorphic adenoma (Fig. 4).

Tumor was noted to involve the underlying bone (pT4a) and all resection margins were free of tumor. The nodal yield of the tumor was 41 and none of the nodes were involved by the tumor (pN0). On immunohistochemical staining: S100 was positive, p40 was weakly

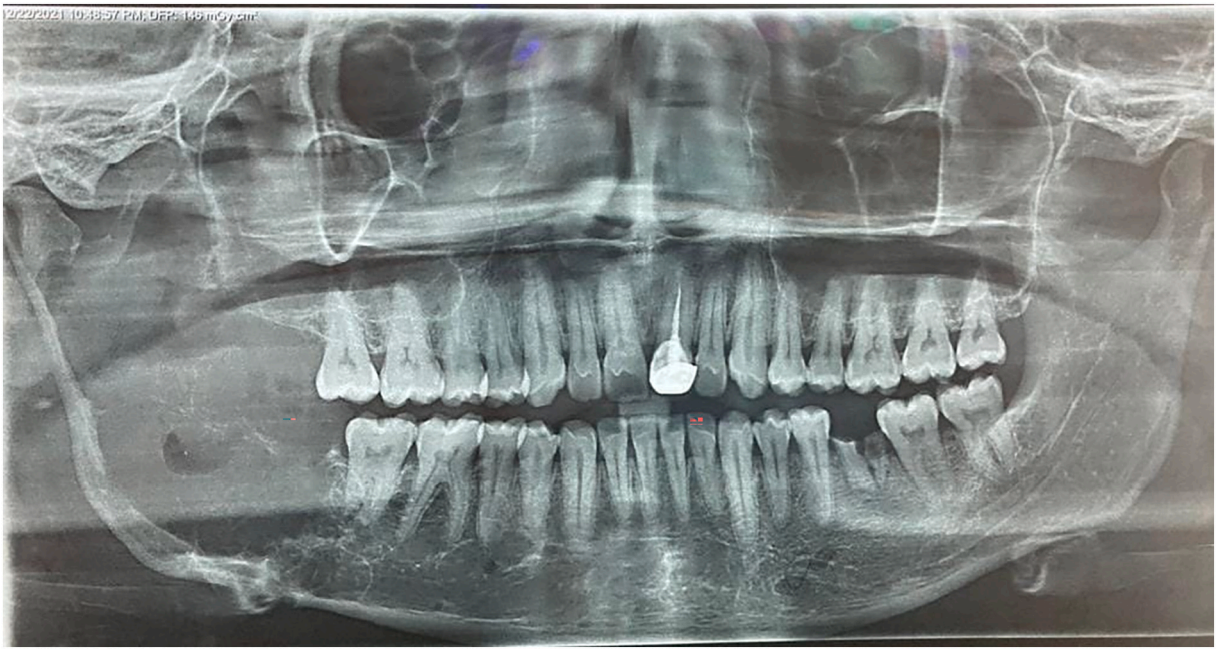

Fig. 1. Orthopantomogram of the patient showing radiolucent lesion in the right mandible.

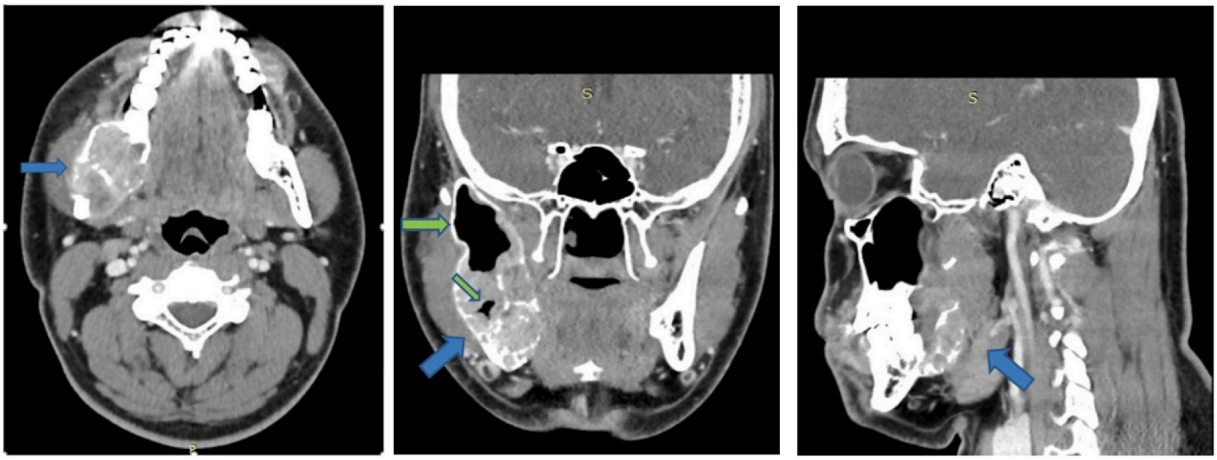

Fig. 2. Axial, coronal and sagittal sections of CT. Blue arrows pointing to the tumor and green arrows pointing to gas within the tumor.

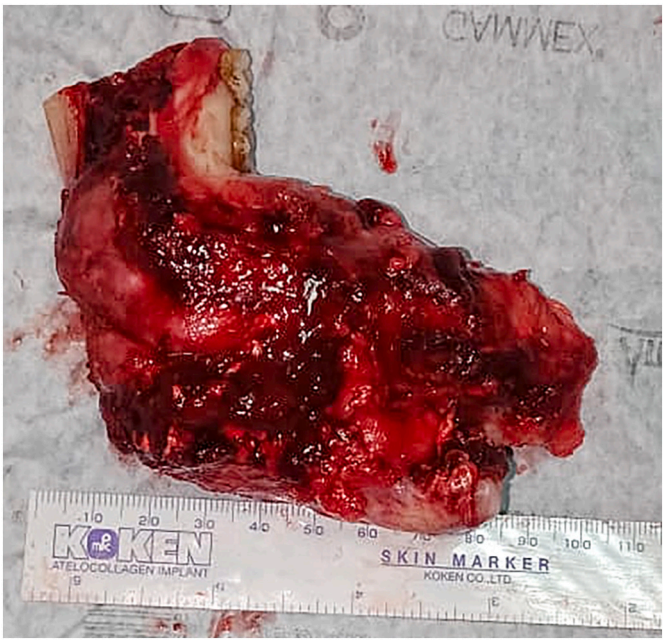

Fig. 3. Gross specimen of resected right mandible.

positive and Mucicarmine was negative. The pathological staging was Stage IVa (pT4aN0). The post operative recovery was uneventful. The case was again discussed in MDT and a decision was made to give post operative radiotherapy 20 fractions over 6 weeks. The patient has completed his radiotherapy and is currently under surveillance. His definitive dental rehabilitation has been delayed till the radiation reaction settles. Patient is tolerating well with the soft diet, has no functional deficit and resumed the normal work without any constraints. The post operative OPG shows well aligned fibular graft at the site of defect fixed with recon plates (Fig. 5). The patient has stable occlusion and >2 cm mouth opening with optimal functional outcomes after surgery and radiotherapy (Figs. 6, 7).

3. Discussion

Carcinoma ex pleomorphic adenoma (CEPA), as the name suggests, is a malignant transformation originating from pleomorphic adenomas. Pleomorphic adenomas are benign mixed tumors that may arise from any major or minor salivary gland tissue; predominantly found in the parotid gland (84 %) followed by submandibular gland (8 %) and other salivary glands (6.5 %) [12]. The classical PA is a well lobulated benign tumor having a pseudo-capsule. It occurs in the superficial lobe of the parotid gland and with good surgical technique can be removed with preservation of the main trunk of facial nerve and its branches. Among the unusual sites of presentation, pleomorphic adenomas may arise from the upper lip followed by buccal mucosa and tongue; infrequent cases

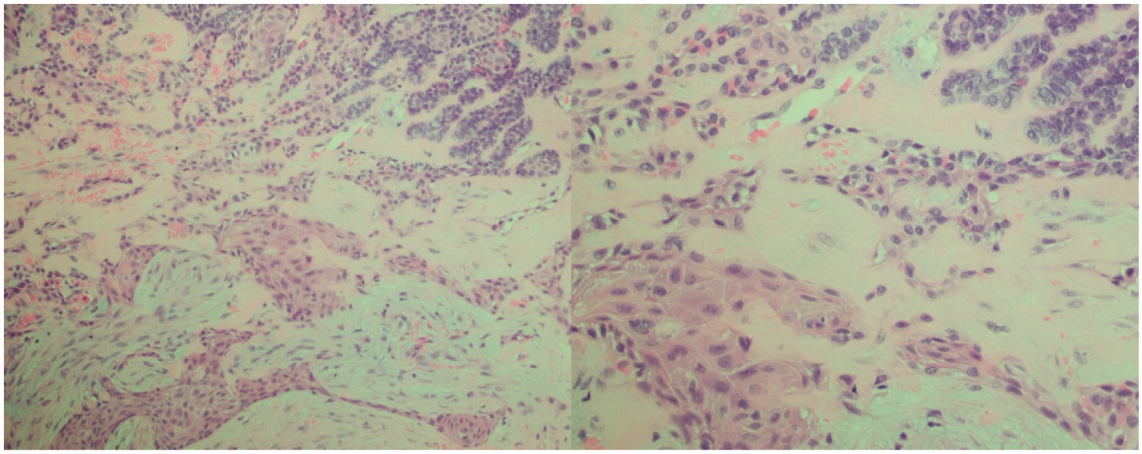

Fig. 4. Histological findings of the tumor stained with hematoxylin and eosin (H&E). The sections revealed ductal and myoepithelial cells arranged in bi-layered tubular structures in myxoid stroma with invasive nests of polygonal squamoid cells.

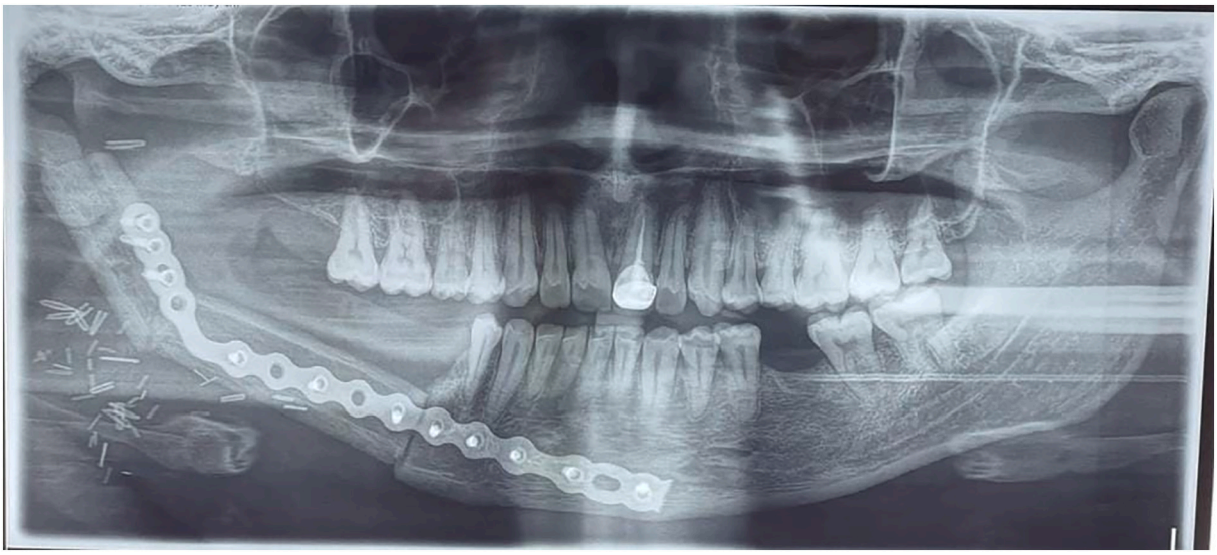

Fig. 5. Post operative orthopantomogram of patient showing right mandibular defect reconstructed with free fibular graft.

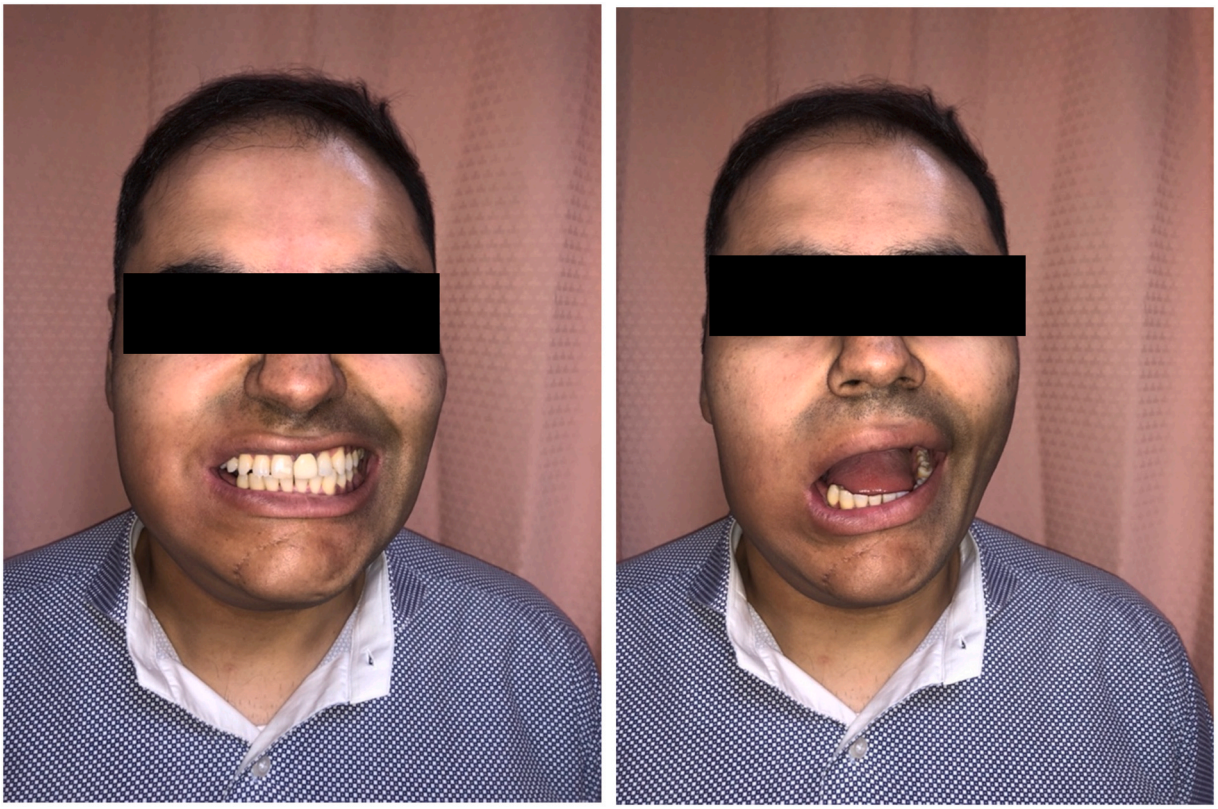

Fig. 6, 7. Stable occlusion and adequate mouth opening post surgery and radiotherapy.

were reported at the maxillary sinus and in the pterygopalatine space as well [13]. These are consistent with the location of minor salivary glands, most of which are concentrated along the buccal mucosa, labial mucosa, lingual mucosa, soft/hard palate and floor of mouth [14].

The prevalence of CEPA transformation from pleomorphic adenoma is 1.5 % within the first 5 years of diagnosis, going up to 10 % after 15 years [15]. The true rate of malignant transformation in recurrent pleomorphic adenoma is reported to be 3.3 % [16]. Based on morphological and immunohistochemical features, CEPAs were classified into carcinomas with luminal differentiation (CEPA-LD) and non-luminal differentiation (CEPA-NLD) [20]. In majority of the cases (75 %), luminal epithelial cells undergo malignant transformation [20]. Carcinomatous component of CEPA is also classified in to 3 sub-classes; non-invasive, minimally invasive and invasive CEPA, based on capsular invasion of the malignant element of the tumor [20]. Tumors with invasion >1.5 mm, regardless of histopathological subtype, are associated with a worse prognosis [21].

Classically seen to affect major salivary glands, PA and CEPA can occur in a host of unusual anatomic sites. We report a case of an intraosseous carcinoma ex pleomorphic adenoma (CEPA) of the mandible.

It is thought that ectopic entrapment of salivary tissue [17] or developmentally included embryonic remnants of submandibular glands within recesses or lacunae of the mandibular bone could explain the intraosseous origin of a salivary gland tumor in the mandible [18]. Carcinoma ex pleomorphic adenomas within the mandible are extremely rare and only a few cases have been reported to date [17]. CEPA can present as an asymptomatic mass but may also present with new onset of pain, facial nerve paralysis, skin ulceration or fixation, or lymphadenopathy [15] depending on the anatomical site. A sudden increase in size of a longstanding pleomorphic adenoma can raise clinical suspicion of carcinoma ex pleomorphic adenoma [19], as in the case of our patient.

True intraosseous tumors of mandible are very rare. These include primary intraosseous adenoid cystic carcinoma, squamous cell carcinoma, schwannoma and peripheral nerve sheath tumor to name a few. The criteria to diagnose true intra osseous carcinoma expleomorphic adenoma is based on certain characteristics that include a) presence of a lesion in maxilla or mandible with no evidence of lesion in the salivary gland substance b) osteolytic appearance of bone on imaging c) no evidence of oral or mucosal lesion d) no clinical or histological evidence of metastatic or primary odontogenic lesion and e) confirmation of the diagnosis on final histopathology [7]. In our case, the patient had presented with right mandibular swelling. An aggressive lesion causing mandibular bony destruction was observed on imaging. The major bulk of the tumor was confined to the mandible. There was cortical erosion visible on the CT scan and the tumor had gone into the surrounding soft tissue through defects in the cortices of mandible. On incisional biopsy under local anesthesia the lesion came out to be pleomorphic adenoma. The diagnosis was revised to CEPA after re-biopsy of the tumor under general anesthesia. Intra operatively, the tumor was observed to be originating from inside the mandibular bone. There is very less probability of the tumor originating from minor salivary tissue of the oral sub mucosa because the major bulk was intraosseous and the soft tissue component was minimal and was related to the cortical defects caused by the invading tumor from inside the bone. Moreover, true gingival salivary gland tumors invading bone are even more rare than intraosseous tumors.

Since carcinoma ex pleomorphic adenoma (CEPA) arises from primary or recurrent pleomorphic adenoma, therefore it poses a diagnostic challenge for histopathologists [23]. Similarly, in this case, the initial diagnosis of the lesion being pleomorphic adenoma was later changed to carcinoma ex pleomorphic adenoma. One of the reasons of misdiagnosis could be the presence of residual pleomorphic component within the lesion. Therefore, pleomorphic adenoma on the initial biopsy should not exclude the possibility that the lesion can turn out to be malignant on final histopathology [23]. Carcinomatous component of CEPA is usually classified in to 3 sub-classes which include a) non-invasive b) minimally invasive and c) invasive. These are based on capsular invasion of the malignant element of the tumor. As the name suggests, there is no penetration of malignant element in non-invasive type. However, there is penetration of $<$1.5 mm and $>$1.5 mm in minimally invasive and invasive type respectively. True intraosseous tumors of mandible are very rare. The differentials include primary intraosseous adenoid cystic carcinoma, squamous cell carcinoma, schwannoma and peripheral nerve sheath tumor to name a few. Surgical excision with post operative radiotherapy is the mainstay of treatment once diagnosed [22].

Intra osseous tumors are rare, they can behave vary aggressively with possibility of metastasis. The radiographic picture of primary tumor/recurrence can mimic odontogenic cyst/tumor; therefore, a sinister disease process should always be kept in mind. In the post operative period, regular follow up is required to treat any recurrence. The recurrence rate for such disease has not been documented.

4. Conclusion

Intra osseous CEPA is a very rare tumor. Intra bony tumors which rapidly increase in size have signs and symptoms of nerve involvement and cause bony destruction should have a high suspicion of index of malignancy. Therefore, biopsy must be correlated with clinical and radiological features. Regular follow up is necessary to detect any recurrence promptly.

Consent

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CRediT authorship contribution statement

1. Dr. Shayan Khalid Ghaloo – Study concept, writing the paper
2. Dr. Muhammad Umar Qayyum – Writing the paper, Data collection
3. Dr. Omair Ahmed Shaikh – Writing the paper, Data collection
4. Dr. Muhammad Faisal – Writing the paper
5. Dr. Ahmed Ali Keerio – Data collection
6. Dr. Raza Tasawur Hussain – Writing paper.

Declaration of competing interest

None.

References

[1] H. Leverstein, J.E. van der Wal, R.M. Tiwari, I. van der Waal, G.B. Snow, Surgical management of 246 previously untreated pleomorphic adenomas of the parotid gland, Br. J. Surg. 84 (3) (1997 Mar) 399–403.
[2] F.A. de Oliveira, E.C. Duarte, C.T. Taveira, A.A. Máximo, E.C. de Aquino, C. Alencar Rde, E.F. Vencio, Salivary gland tumor: a review of 599 cases in a brazilian population, Head Neck Pathol. 3 (4) (2009 Dec) 271–275.
[3] R.L. Witt, The significance of the margin in parotid surgery for pleomorphic adenoma, Laryngoscope 112 (12) (2002 Dec) 2141–2154.
[4] B.W. Neville, D.D. Damm, C.M. Allen, ChiAC., in: Oral and Maxillofacial Pathology, second edition., John Schrefer, Philadelphia, 2002, pp. 410–413.
[5] H. Laccourreye, O. Laccourreye, R. Cauchois, V. Jouffre, M. Ménard, D. Brasnu, Total conservative parotidectomy for primary benign pleomorphic adenoma of the parotid gland: a 25-year experience with 229 patients, Laryngoscope 104 (12) (1994 Dec) 1487–1494.
[6] F.L. Shoukair, A. Maly, T.K. Haran, N. Hirshoren, J. Abu Tair, Maxillofacial diagnostic features of the enigmatic metastasizing pleomorphic adenoma, Int. J. Oral Maxillofac. Surg. 49 (7) (2020 Jul) 841–847.
[7] D. Zhao, H. He, M. Fang, M. Liu, B. Ji, Z. He, Primary central carcinoma ex pleomorphic adenoma of the mandible: report of a rare case and literature review, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 112 (2) (2011 Aug) 24–28.
[8] M. Nadershah, A. Alshadwi, A. Salama, An unusual case of carcinoma ex pleomorphic adenoma of the parotid metastasizing to the mandible: case report and review of the literature, J. Oral Maxillofac. Surg. 71 (2) (2013 Feb) 437–442.
[9] D. Khanna, T. Chaubal, R. Bapat, A.M. Abdulla, S.T. Philip, S. Arora, Carcinoma ex pleomorphic adenoma: a case report and review of literature, Afr. Health Sci. 19 (4) (2019 Dec) 3253–3263.
[10] K. Okano, M. Ishida, K. Sandoh, T. Fujisawa, H. Iwai, K. Tsuta, Cytological features of carcinoma ex pleomorphic adenoma of the salivary glands: A diagnostic challenge, Diagn Cytopathol. 48 (2) (2020 Feb) 149.
[11] C.C. Haltiner, S. Betz, J. Smith, B. Nelson, A.A. Ambrosio, Carcinoma ex-pleomorphic adenoma diagnosis during global health engagement operations, Mil. Med. 186 (Suppl 1) (2021 Jan 25) 828–832.

[12] M.R. Bokhari, J. Greene, Pleomorphic Adenoma, in: StatPearls [Internet], StatPearls Publishing, Treasure Island (FL), 2022 Jul 4, 2022 Jan.
[13] H. Nouri, T. Ziad, Y. Rochdi, L. Aderdour, A. Raji, Adénome pléomorphe à localisation inhabituelle: à propos d'une série de sept cas [unusual location of pleomorphic adenoma: a series of 7 cases], Rev. Laryngol. Otol. Rhinol. (Bord). 135 (4–5) (2014) 201–205.
[14] A.T. Kessler, A.A. Bhatt, Review of the major and minor salivary glands, part 1: anatomy, infectious, and inflammatory processes, J. Clin. Imaging Sci. 15 (8) (2018 Nov) 47.
[15] J.R. Wang, D. Bell, R. Ferrarotto, R.S. Weber, S.Y. Su, Surgery of the Salivary Glands (2021) 286–301.
[16] J. Thielker, M. Grosheva, S. Ihrler, A. Wittig, O. Guntinas-Lichius, Contemporary management of benign and malignant parotid tumors, Front Surg. 11 (5) (2018 May) 39.
[17] L. Aghaghazvini, S. Aghaghazvini, Intraosseous pleomorphic adenoma of the mandible, Iran. J. Radiol. 12 (1) (2015 Jan 1) 6921.
[18] Z.H. Ren, D. Chickooree, J.B. Liu, H.J. Wu, Primary intraosseous ACC of mandible of possible salivary origin: a rare clinical entity, Int. J. Surg. Case Rep. 5 (5) (2014) 222–225.
[19] A. Gupta, S. Koochakzadeh, D.M. Neskey, S.A. Nguyen, E.J. Lentsch, Carcinoma ex pleomorphic adenoma: a review of incidence, demographics, risk factors, and survival, Am. J. Otolaryngol. 40 (6) (2019) 102279. Nov-Dec.
[20] K.P. Priyanka, U. Divya, S. Majumdar, R.V. Sridhar, Carcinoma ex pleomorphic adenoma- histopathology the gold standard, Austin Clin. Microbiol. 1 (1) (2016) 1005.
[21] H.C. de Souza LB, R. de Almeida Freitas, Extracapsular invasion: a potential prognostic marker for carcinoma ex-pleomorphic adenoma of the salivary glands? A systematic review, J Oral Pathol Med. 48 (6) (2019 Jul) 433–440.
[22] R. Keerthi, R.P. Raut, N. Vaibhav, A. Ghosh, Carcinoma ex pleomorphic adenoma: diagnostic dilemma and treatment protocol, Indian J. Dent. 5 (3) (2014 Jul) 157–160.
[23] R.A. Agha, M.R. Borrelli, R. Farwana, K. Koshy, A. Fowler, D.P. Orgill, For the SCARE Group, The SCARE 2018 statement: updating consensus Surgical CAse REport (SCARE) guidelines, Int. J. Surg. 60 (2018) 132–136.