Sclerosing Mucoepidermoid Carcinoma of the Submandibular Gland Presenting as Chronic Sialadenitis: A Case Report and Review of Literature

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Received: 19 February 2017 / Accepted: 4 May 2017 / Published online: 17 May 2017
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Abstract Sclerosing mucoepidermoid carcinoma of the salivary gland (SMEC) is a rare subtype of mucoepidermoid carcinoma (MEC), first described in 1987 by Chan and Saw. As far as we are aware, only 30 cases have been published since then. Most cases were located in the parotid gland with some cases described in the submandibular and minor salivary glands. SMEC typically presents as a long-standing mass, with a non-specific enhancing appearance on imaging and is often non-diagnostic on fine needle aspiration, making pre-operative diagnosis very difficult. It is characterised by dense sclerosis within an otherwise typical MEC, frequently with lymphoid proliferation and eosinophils at the periphery. The histological diagnosis of SMEC can be challenging, as the sclerosis may obscure the other morphological features, which can lead to misdiagnosis. Grading can also be difficult, and the prognostic value of grading for SMEC remains unclear. Herein is described a new case of SMEC, presenting clinically as chronic sialadenitis in the left submandibular gland of a 41 year old male. A brief literature review and the issues surrounding diagnosis and grading are also discussed.

Keywords Sclerosing mucoepidermoid carcinoma · Mucoepidermoid carcinoma · Salivary gland · Fine needle aspiration · Grading · Prognosis

Introduction

Sclerosing mucoepidermoid carcinoma of the salivary gland (SMEC) is a rare subtype of mucoepidermoid carcinoma (MEC), initially described in 1987 by Chan and Saw [1]. Since the original publication, and as far as we are aware, 30 further cases have been described in the English language literature. 20 of these cases have occurred in the parotid gland, five in the submandibular gland and five in the minor salivary glands. SMEC typically presents as a long standing mass with a non-specific enhancing appearance on imaging [2]. Fine needle aspiration (FNA) is often non-diagnostic [3], making pre-operative diagnosis very difficult. They are commoner in women than men, and the average age of occurrence is 46, with a wide age range, from 16 to 79 [3]. It is generally considered to be a low grade tumour with a good prognosis, which rarely metastasises or recurs. As the name suggests, SMEC is characterised by dense sclerosis within an otherwise typical MEC, frequently with lymphoid proliferation including eosinophils at its peripheral margins [4]. The histological diagnosis of SMEC can be challenging, as the sclerosis may obscure the other morphological features. The prognostic value of the tumour grade in SMEC using current MEC grading systems is unclear [5]. Increased awareness and knowledge of this rare subtype of MEC should guide pathologists to consider and carefully evaluate the possibility of SMEC, when faced with a sclerotic salivary gland lesion, reducing the risk of misdiagnosis.

Case Report

A 41 year old gentleman was referred on a suspected head and neck cancer pathway by his primary physician for

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assessment of a lump located in the left anterior triangle of the neck. The mass had been present for 2 months and was gradually increasing in size. The patient complained of pain over the left side of his neck, radiating to the left ear. He had no relevant medical, drug or allergy history. There was no family history of cancer and his performance status and co-morbidity scores were both zero. On clinical examination, a well-defined mass measuring approximately 1 × 1 cm was present in the left submandibular triangle. On palpation, the mass was firm and fixed to the deeper tissue. There was no lymphadenopathy and the oral cavity and oropharynx appeared normal. There was no paresthesia or facial nerve dysfunction.

Flexible endoscopy showed a normal pharynx and larynx. A computed tomography (CT) scan of his head and neck with contrast was ordered which revealed a well-defined area of calcification within the submandibular gland. This 8 mm focus of coarse calcification was thought to represent a salivary duct stone. Based on the clinical and radiological examination, the provisional diagnosis was left submandibular chronic sialadenitis secondary to sialolithiasis. Given the lack of lymphadenopathy and facial nerve involvement, a complete submandibular gland excision was performed. The submandibular gland was then sent for formal histopathological examination.

Gross pathological analysis showed a submandibular gland measuring 40 × 30 × 20 mm with a smooth, regular surface. The cut surface showed a well-defined calcified area measuring 5 × 5 × 12 mm, located 6 mm from the gland surface. Histological sections showed the calcified area to be a well-defined tumour, with a mainly solid architecture, with scattered cystic foci (Fig. 1). The tumour was composed of prominent hyalinised stroma, within which nests and islands of tumour cells were present, with an

Fig. 1 Tumour with a densely sclerotic stroma and central calcification; H and E ×1.25

infiltrative edge (Fig. 2). The tumour cells were predominantly epidermoid, but mucus cells and intermediate cells were also present (Fig. 3). The stroma contained calcification, but no psammoma bodies or sialolith was identified. At the periphery of the tumour was a dense lymphocytic infiltrate with very few eosinophils (Fig. 4), forming occasional germinal centres (Fig. 5). Prominent hypertrophic nerves were noted in and around the tumour, with no perineural invasion (Fig. 5). No necrosis, mitosis or anaplasia was present. A positive mucin stain (Alcian blue periodic acid schiff, resistant to diastase digestion) confirmed the presence of extracellular and intracellular mucin (Fig. 6). Immunohistochemistry showed the epidermoid and mucus cells were strongly and diffusely positive for BerEP4, while p63 stained the nuclei of occasional epidermoid cells

Fig. 2 Infiltrative edge of the tumour (arrow); H and E ×1.25

Fig. 3 Typical morphology of MEC, with a mixture of epidermoid cells (black arrow), intermediate cells (red arrow) and mucus cells (white arrow); H and E ×40

Fig. 4 Scattered eosinophils present against a lymphoid background; H and E $\times 40$

Fig. 6 Intracellular mucin highlighted with alcian blue; Alcian blue diastase periodic acid schiff $\times 20$

Fig. 5 Hypertrophic nerves, present within and around the carcinoma. Dense lymphoid aggregates with occasional germinal centres are also seen at the tumour periphery; H and E $\times 1.25$

Fig. 7 Occasional p63 positive epidermoid cells; P63 $\times 20$

(Fig. 7). The mucus cells were p63 negative. The tumour was Her-2 negative and MIB-1 showed a low proliferation fraction ($<5\%$). Excision of the tumour was complete with a 2 mm resection margin. Overall, the histological features were considered to be characteristic of SMEC and the carcinoma was considered to be low grade, based on the Modified Healy and Armed Forces Institute of Pathology (AFIP) grading systems [6].

Following the diagnosis, the patient was referred for an orthopantomogram radiograph, CT scan of his chest and an MRI with contrast of his head and neck for postoperative staging. These revealed no radiological evidence of regional lymph node or distant metastasis and the tumour was therefore graded as T1, N0, M0 (TNM 7th edition).

Taking into consideration the favourable histology, the patient's age, and the morbidity of radiotherapy, the head and neck multidisciplinary cancer team recommended close follow-up. At 5 months post operation, the patient demonstrated no clinical or radiologic evidence of disease.

Discussion

MEC of the salivary gland is characterised by cords and sheets of epidermoid, mucus and intermediate cells. Architecturally, it exhibits solid and cystic areas with mucin pools. SMEC is a rare subtype of MEC, which contains, in addition to the usual features, extensive hyalinising sclerosis and lymphoplasmacytic infiltrate [4].

Imaging generally shows a nonspecific, mildly enhancing mass [3]. In this case however, imaging showed a well-circumscribed area of calcification, resembling a stone, leading to the provisional diagnosis of sialadenitis secondary to sialolithiasis. Aspiration cytology typically has limited diagnostic benefit given the hypocellularity and dense fibrotic stroma of the tumour [2]. An FNA was not performed in this case, as it was not clinically indicated with a provisional diagnosis of sialadenitis.

On excision, the histologic features of SMEC can lead to misdiagnosis as it may resemble other entities. For example, the lymphoid aggregates at the periphery may resemble a lymph node metastasis, however, this can usually be excluded by the lack of capsule and subcapsular sinuses [7]. The sclerotic stroma of the tumour can mask the tumour islands, potentially leading to diagnosis of another sclerosing salivary gland lesion, including benign diagnoses such as sclerosing sialadenitis [8]. Therefore, in order to reach a diagnosis of SMEC, it should be considered in the differential for both lymphocytic and sclerotic salivary gland lesions.

When SMEC is identified, the differential diagnoses can be numerous, including other salivary gland lesions with a desmoplastic stroma, such as pleomorphic adenoma, carcinoma ex pleomorphic adenoma, hyalinising clear cell carcinoma and glycogen-rich clear cell carcinoma [9]. Chronic sclerosing sialadenitis shares both the lymphocytic infiltrate and sclerotic stroma of SMEC, and cystadenocarcinoma has a similar cystic architecture [2] while sialometaplasia has mucin cells and extravasated mucin [10]. Despite this wide differential, including both benign and malignant entities, in the majority of cases these diagnoses each have clear distinguishing features, allowing clear-cut differentiation from SMEC.

There is debate regarding the cause of the sclerosis seen in SMEC. Various hypotheses suggest that it may be a response to extravasated mucin or ruptured cysts [4, 8, 11], due to tumour infarction [1] or caused by eosinophils [12]. The fact that some cases do not show prominent eosinophils argues against the eosinophil theory, and Ide et al. [5] argue that the eosinophils are not prominent enough to cause sclerosis. It has also been suggested that the lymphoid infiltrate may occur as a reaction to ruptured cysts, and it has been postulated that similar lesions which lack this infiltrate may be older, therefore the inflammatory component has resolved [11]. Another proposal from Tian et al. [13], suggests that the sclerosis is caused by IgG4-positive plasma cells, which they found in high numbers within the lymphoid infiltrate of the tumour.

MEC tumours are usually classified as low grade and of the cases of SMEC described so far; 20 were low grade, six intermediate grade and three high grade (one case did not provide a grade). In this case, the tumour is low grade,

using the current classification systems for MEC (AFIP and Modified Healy grading systems). The suitability of these grading systems has not yet been determined for SMEC, and some confounding factors may have an effect, for example the sclerotic stroma reduces the number of tumour cells per high power field, leading to reduced mitotic counts. Additionally, using the Modified Healy classification [6], peripheral chronic inflammation is a feature of intermediate grade, whereas the presence of minimal chronic inflammation is a high grade feature. Whether the use of these systems has prognostic value in SMEC remains to be seen [14].

Of the 30 reported cases of SMEC, 20 have provided follow-up data, ranging from 3 months to 17 years. Four cases report recurrence or metastasis, occurring from 3 to 15 years post-diagnosis [12, 15, 16]. The grading in these cases includes two low grade, one intermediate grade and one high grade tumour. While the data is limited, this brings into question the use of current grading systems as an indicator of prognosis. It appears that MIB-1 may not be a reliable prognostic indicator, as a case with a MIB-1 of 7.2% led to death 5 years after diagnosis [12], yet another case with a MIB-1 of 5% had no evidence of recurrence or metastasis at 3 years [12]. In addition, Veras et al. [4] reported four cases, three of which had a MIB-1 of <5% and no recurrence or metastasis at 4 months, 11 and 17 years and another case with a MIB-1 of 12% and no recurrence or metastasis at 8 months. The current case shows a MIB-1 of <5%. This evidence does not seem sufficient to conclude whether MIB-1 is in fact a reliable prognostic marker. Overexpression of Her-2/neu is a poor prognostic factor in MEC, however Veras et al. [4] found no relationship between grade and Her-2/neu expression in SMEC. Fadare et al. [11] suggest that tumour size may be a prognostic factor, similar to MEC, however, there is no clear correlation apparent using the current data (Table 1). Overall, it is currently not possible to comment on the prognostic factors of SMEC due to the rarity of this variant. Also, in many cases long term follow up data has not been published, with many cases being reported with no recurrence or metastasis over months or less than 5 years. Only three cases report 10 or more years of follow up, one of which showed recurrence at 15 years, emphasizing the importance of long term follow up data [4, 5].

A specific treatment strategy for SMEC has not yet been devised, and as such, the treatment has differed according to local preference. This variation probably reflects the limited amount of evidence available to clinicians with regard to the natural course of this disease. The reported cases so far show a variety of approaches. Veras et al. [4] treated conservatively with a superficial parotidectomy and reported complete excision of the tumour in all four of their cases. Alternatively, Shinhar

Table 1 Reported cases of sclerosing mucoepidermoid carcinoma of the salivary glands

	Source	Age/sex	Site	Size (cm)	Eos	Grade	Treatment	Follow up
1	Chan and Saw [1]	36/F	Parotid	2.2×1.7	–	Low	Superficial parotidectomy	Not available
2	Muller et al. [9]	17/F	Parotid	2	+	Inter	Superficial parotidectomy	Not available
3	Muller et al. [9]	60/F	Parotid	1.5	+	Inter	Resection and radiation	Not available
4	Sinha et al. [17]	65/M	Minor salivary gland	6	–	High	Resection and radiation	Not available
5	Urano et al. [12]	57/F	Parotid	2.5×2	+	Low	Superficial parotidectomy	Metastasis at 3 years
6	Urano et al. [12]	43/M	SMG	4.5×2.5	+	Low	Complete excision	Metastasis at 5 years and death
7	Fadare et al. [11]	44/F	Parotid	1.5	–	Low	Complete parotidectomy	No evidence of recurrence or metastases at 7 years
8	Ide et al. [7, 16]	28/M	Minor salivary gland–intraoral	2.2	+	Inter	Complete excision	High grade recurrence of non-sclerosing MEC at 15 years
9	Heavner and Shah [10]	23/F	Parotid	2	+	Low	Complete parotidectomy and radiation	No evidence of recurrence or metastases at 1 year
10	Lee and Kwan [16]	62/F	Parotid	N/A	N/A	High	Superficial parotidectomy	Recurrence at 4 year follow-up
11	Veras and Sturgis [4]	70/F	Parotid	4	+	Low	Superficial parotidectomy	No evidence of recurrence or metastases at 11 years
12	Veras and Sturgis [4]	37/M	Parotid	2.2	+	Low	Superficial parotidectomy	No evidence of recurrence or metastases at 17 years
13	Veras and Sturgis [4]	49/F	Parotid	1.7	+	Low	Superficial parotidectomy	No evidence of recurrence or metastases at 4 months
14	Veras and Sturgis [4]	16/F	Parotid	2	+	Inter	Superficial parotidectomy	No evidence of recurrence or metastases at 8 months
15	Kim et al. [18]	51/F	Parotid	1.4	– (few)	Low	Resection and radiation	No evidence of recurrence or metastases at 3 months
16	Aguiar and Bernardes [19]	43/F	Parotid	4	–	Low	Not available	Not available
17	Shinhar [7]	57/F	Parotid	2	–	Inter	Superficial Parotidectomy and radiation	No evidence of recurrence or metastases at 3 years
18	Mendelson and al-Macki [2]	21/F	Parotid	1.5	–	Low	Superficial parotidectomy	No evidence of recurrence or metastases at 3 years
19	Kayal et al. [20]	24/F	Minor salivary glands–palate	4.4×4.2	–	Low	Complete parotidectomy with level II neck dissection	Not available
20	Tian and Yakirevich [13]	42/F	Parotid	1.5	–	Low	Local excision	No evidence of recurrence or metastases at 19 months
21	Tian and Yakirevich [13]	52/F	Parotid	1.4	–	Low	Local excision	No evidence of recurrence or metastases at 31 months

Table 1 (continued)

	Source	Age/sex	Site	Size (cm)	Eos	Grade	Treatment	Follow up
22	Tian and Yakirevich [13]	62/F	Parotid	2	–	Low	Local excision	Not available
23	Tian and Yakirevich [13]	28/M	Parotid	1.2	–	Low	Local excision	No evidence of recurrence or metastases at 8 months
24	Tian and Yakirevich [13]	32/M	SMG	1.5	–	Low	Complete excision	No evidence of recurrence or metastases at 15 months
25	Mardi and Madan [8]	58/M	SMG	2.8×2.3	–	High	Complete excision with right lymph node levels I-IV (positive nodes)	Not available
26	Mardi and Madan [8]	65/M	SMG	3×3	–	Low	Complete excision	Not available
27	Tasaki et al. [21]	79/M	SMG	5.6	+	Low	Complete excision	No evidence of recurrence or metastasis at 15 months
28	Boaz et al. [22]	73/F	Minor salivary glands–palate	6.5×3.5×2	–	Low	Subtotal right maxillectomy	No evidence of recurrence or metastases at 6 months
29	Lohiya et al. [23]	45/F	Minor salivary gland–retromolar	4×5	–	Inter	Hemimandibulectomy	No evidence of recurrence or metastasis at 12 months
30	Bhat et al. [2]	32/M	Parotid	4.5×3×2.5	–	N/A	Superficial parotidectomy	No evidence of recurrence or metastasis at 6 years
31	Present case, 2015	41/M	SMG	0.4×0.3×0.2	+	Low	Complete excision	No evidence of recurrence or metastasis at 5 months

Eos eosinophils, *F* female, *Inter* intermediate, *M* male, *SMG* submandibular gland, *N/A* not available

et al's treatment modality included superficial parotidectomy with postoperative radiotherapy despite negative surgical margins, as the lesion was classified as intermediate grade [7]. Both reported no metastasis or recurrence. Urano et al. [12] performed total submandibular gland excision without radiotherapy but metastasis was discovered 5 years later. Tian et al. [13] elected to treat conservatively with a wide local excision of the submandibular gland without radiotherapy and there has been no recurrence or metastases at 15 months. Heavner et al. [10] recommend complete surgical excision with radiotherapy in cases with positive or close resection margins, with serial MRI imaging and follow-up of the lymphatics and chest. In our case, the patient had complete submandibular excision without postoperative radiotherapy as the carcinoma was completely excised and low grade. The data on this rare subtype of MEC is limited, and the optimum treatment modality is therefore difficult to establish, but currently this should be discussed locally and a treatment plan devised according to the features of an individual case.

Conclusion

In conclusion, we describe a rare case of sclerosing mucoepidermoid carcinoma, which presented as chronic sialadenitis, in contrast to previously described cases, which presented as a mass. It was treated with complete excision and showed no evidence of recurrence or metastasis at 5 months. The available literature describes SMEC as a distinct histological subtype of MEC with characteristic histopathological features. The sclerosis and inflammatory infiltrate of the tumour may cause confusion with other diagnoses with similar features, including both benign and malignant entities. A pre-operative diagnosis may be misleading, due to a non-specific appearance on imaging and typically a hypocellular FNA. The cause of the sclerosis and inflammatory infiltrate has not been definitively determined, but various theories have been suggested, including ischaemia, cyst rupture and extravasated mucin, and eosinophils. The grading systems currently in use for MEC do not appear to provide prognostic information for this subtype, and more research is required to determine

whether certain features such as MIB-1/proliferation fraction, tumour size or Her-2/neu expression could be used as independent prognostic markers. Very little data is available on the optimal treatment modalities for SMEC, but it is hoped that each case is discussed at local multidisciplinary meetings and an appropriate treatment plan may be devised. Certainly, long term follow up should be integral to management of SMEC, particularly as metastasis has been documented 15 years after initial presentation. Increased awareness of this rare entity will hopefully guide pathologists to consider SMEC when faced with a sclerotic salivary gland lesion.

Compliance with Ethical Standards

Conflict of interest All authors declares that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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