CASE REPORT

Parotid Sebaceous Carcinoma in Patient with Muir Torre Syndrome, Caused by MSH2 Mutation

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Abstract Sebaceous carcinoma of parotid gland are extremely rare with only 29 cases reported so far. The development of parotid sebaceous carcinoma in association with mutation in the mismatch repair gene that causes Muir Torre Syndrome (MTS), a subset of Lynch Syndrome, is still unclear. This study describes such a case and reviews the literature to see if an association between parotid sebaceous carcinoma and multiple visceral malignancies seen in Lynch Syndrome has ever been described. MTS represents a small subset of the Hereditary Non Polyposis Colorectal Carcinoma family, thought to be a subtype of Lynch Syndrome, where patients are prone to develop multiple visceral cancers involving gastrointestinal and genitourinary tract along with sebaceous and non-sebaceous tumours of the skin. MTS is a rare hereditary, autosomal dominant cancer syndrome caused by Microsatellite Instability and defect in DNA mismatch repair protein. The germline mutation involves mostly hMSH2 and hMLH1 genes. In MTS the skin of the head

and neck area with the periocular region in particular, is affected but sebaceous carcinomas of the parotid associated with visceral malignancies has not yet been reported in literature. Here we report an index case of sebaceous carcinoma of parotid gland in a patient with MTS.

Keywords Sebaceous carcinoma · Muir Torre and Lynch syndrome · Microsatellite instability · Parotid gland

Introduction

Sebaceous carcinomas of parotid gland are extremely rare with only 29 cases reported so far [25, 26]. The development of parotid sebaceous carcinoma in association with mutation in the mismatch repair (MMR) gene that causes Muir Torre Syndrome (MTS) has not been described.

MTS, a variant of Lynch Syndrome, is an autosomal dominant geno-dermatosis with at least one sebaceous neoplasm and visceral malignancy [1–5]. Males are more commonly affected with male to female ratio of 3:2 [4]. Sebaceous neoplasms are diagnosed at a mean age of 53 years and visceral malignancies at the mean age of 50 years [2–4]. The common cutaneous malignancies associated with MTS are sebaceous adenomas, sebaceous carcinoma/lymphadenocarcinoma sebaceous epithelioma, keratoacanthoma and basal cell carcinoma with sebaceous differentiation [5]. The most common visceral malignancy associated with MTS is Colorectal Adenocarcinoma followed by genitourinary malignancies [4, 6, 7]. The underlying genetic abnormality in MTS is the Microsatellite Instability caused by DNA mismatch repair gene mutation [8–15]. Germline mutation in hMSH2 and hMLH1 genes are often associated with this disorder [5, 6, 16, 17]. The incidence of Muir Torre Syndrome is low and

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one of the largest reviews published in 1999 showed 205 cases worldwide [18]. In the UK, one of the largest Regional Genetics Service at St Mary's Hospital covering the population of the North West England has two hundred and twenty-four Lynch Syndrome families with proven pathological mutations in the MMR genes [19]. The most common site for sebaceous neoplasms in Muir Torre Syndrome is the eyelids and nose [20–22] but to the best of our knowledge and our extensive review of the literature, no cases of sebaceous carcinoma involving parotid in Muir Torre Syndrome have been described [18–29].

Here we report an index case of Muir Torre Syndrome associated with sebaceous carcinoma of left parotid.

Case Report

A 67 year old female with a past history of *peri-ampullary*/pancreatic adenocarcinoma in 1994, colonic carcinoma in 1995 and gastric carcinoma in 2003 presented with a painless swelling in the left parotid region in 2015. From 1996 to 2013 she developed multiple sebaceous adenomas predominantly involving the skin of the head and neck region and four carcinomas (*three* squamous cell carcinomas from right sternum in 2004, right frontal area, in 2005 and skin from upper lip, in 2006 respectively). The fourth carcinoma was in *her* scalp in 2011 and reported as sebaceous carcinoma on an incisional biopsy. No residual carcinoma was found in the subsequent skin excision. In 1996 the patient was diagnosed with Lynch Syndrome and since then put on regular follow up. The clinical notes of her family history showed 5 types of malignancies in her father.

A FNA was performed from the left parotid swelling and the patient underwent superficial parotidectomy.

Materials and Methods

The pancreatic and colonic resection specimens removed in 1994 and 1995 respectively were not available for review but we retrieved the skin specimens from 2000 to 2015 and the total gastrectomy specimen in 2003.

Results

Histology review confirmed a T2 N1 mucinous carcinoma with signet ring cells of the stomach. The diagnoses of sebaceous hyperplasia (Fig. 1) and sebaceous adenomas of the skin were also confirmed.

The carcinoma removed in 2004 from the skin of right sternum was an excised, moderately differentiated

Fig. 1 Skin excision from chin showing sebaceous hyperplasia, a hallmark of Muir Torre Syndrome. Dark and light areas corresponding to germinative cells and sebaceous cells with cytoplasmic lipid microvesicles are seen

squamous cell carcinoma with evidence of keratinisation, 4 mm in depth. Equally the diagnosis of an *excised* well differentiated keratinising squamous cell carcinoma, 3.8 mm thick, of the right frontal area in 2005 was also confirmed.

The carcinoma from the skin of upper lip in 2006 was also well differentiated, 2.9 mm in *greatest dimension* and completely excised. None of them *had* evidence of sebaceous differentiation.

The biopsy *review* taken in 2011 from the scalp confirmed sebaceous carcinoma (Fig. 2a, b) but the subsequent biopsy included scar tissue only. The left parotid FNA showed a mixture of lymphocytes, *histiocytes* and occasional benign cells. It was not diagnostic but the possibility of Warthin's tumour was raised.

The superficial parotidectomy specimen was received in *two pieces measuring* 40 × 32 × 18 mm and 28 × 18 × 13 mm, respectively. The larger specimen included a *circumscribed* nodule, 13 mm with a pale cut surface. The remainder of the specimen was composed of unremarkable lobular glandular tissue.

Microscopy showed an expansile tumour with pushing margins (Fig. 3a). The interphase between carcinoma and salivary gland was mostly composed of dense fibrous tissue (Fig. 3b) but focally there was lymphocytic infiltrate (Fig. 3c). Tumour cells were arranged in lobules showing marked pleomorphism and up to five mitoses per high power field (Fig. 4b). There was abundant necrosis and calcification (Fig. 4a). The carcinoma showed evidence of sebaceous differentiation characterised by outer germinative layer and inner layer of polyhedral cells with microvesicular cytoplasm due to presence of lipids in individual cells (Fig. 5). Immunohistochemistry for CK 7 showed positive staining in

(a)

(a)

(b)

(b)

Fig. 2 a, b 3.2 × 1.7 mm sebaceous carcinoma scalp biopsied in 2011. There is evidence of sebaceous differentiation with marked nuclear pleomorphism and mitoses (**b**). No residual carcinoma was found in the subsequent surgical specimen

tumour cells and normal parotid gland suggesting primary salivary gland origin (Fig. 6). There was no evidence of underlying lymph node, perineural or vascular invasion present. Periodic Acid Schiff Diastase (PAS-D) did not reveal any mucous in the tumour cells. Single cell keratinisation or keratin pearls were not seen.

The case was reviewed by a pathologist with an interest in salivary gland pathology and the diagnosis of sebaceous carcinoma was confirmed.

Discussion

The sebaceous *carcinomas* of salivary glands are extremely rare [30]. In a recent review, Gnepp found only 44 cases of sebaceous carcinoma of which 29 arose in the parotid

(c)

Fig. 3 a–c Sebaceous carcinoma of parotid gland resected in 2015. The tumour has an expansile growth pattern with pushing margins. The interphase between carcinoma and salivary gland is mostly composed of dense fibrous tissue (**b**) but focally there is a lymphocytic infiltrate (**c**)

Fig. 4 **a, b** Sebaceous carcinoma of parotid gland. The tumour shows extensive necrosis and calcification. The carcinoma is arranged in a lobulated pattern (**b**). Mitoses are seen in cells with sebaceous differentiation (*inset*)

gland, 8 in the oral cavity, 3 in the submandibular gland, and 1 from sublingual gland. The remaining 3 were from hypopharynx, epiglottis, and vallecula [26].

The rarity of sebaceous carcinoma of salivary glands is in contrast with the fact that sebaceous glands are commonly found either as isolated cells in the wall of intercalated and striated ducts of parotid or as well defined sebaceous gland surrounded by a basal membrane [31].

On the other hand, intraoral salivary glands containing sebaceous glands (so called Fordyce granules) are seen in up to 80 % of the general population [32].

In the last decade it has also become known that the number of Fordyce granules is increased in patients with Lynch Syndrome with a 50- to 90-fold greater frequency as compared to the general population [33]. On the basis of these *observations* we expected to find more sebaceous

Fig. 5 Sebaceous carcinoma of parotid gland. Characteristic combination of *dark* (germinative) and *light* (sebaceous) cells. Polyhedral cells with microvesicular cytoplasm due to presence of lipids

Fig. 6 Immunohistochemistry shows staining for CK 7 in tumour cells (*left*) and compressed salivary ducts (*right*)

neoplasms of salivary glands and in patients with Muir Torre Syndrome in particular [33].

Our review of the literature (Table 1) aimed to see if there was an association between parotid sebaceous carcinoma with any syndrome or visceral malignancies [25, 26, 34–45], and produced no results which is in agreement with Gnepp who also did not find any similar association [25, 26].

Muir Torre Syndrome represents a small subset of the Hereditary Non Polyposis Colorectal Carcinoma (HNPCC) family where patients have a combination of sebaceous and non-sebaceous skin *tumours* associated with internal malignancies. Muir Torre Syndrome results from defective

Table 1 Summary of reported cases of sebaceous carcinoma of parotid

No	Author	Sex/age/ location	Duration of symptom	Pathology	Follow up	Associated tumours
1	Gnepp et al. [25, 26]	M/ 71/parotid	–	Circumscribed lobulated mass with moderate pleomorphism, necrosis, mitosis	Not available	None
2		F/ 17/parotid	6 months	Partially circumscribed 3 × 2.5 × 5.0 mass with marked anaplasia with necrosis and mitosis	NED at 6.7 years	
3		M/66/right parotid	Several months	6 cm ill defined mass with necrosis, mitosis, moderate pleomorphism	NED at 4.7 years	
4		F/51/right parotid	5 years	Circumscribed 2 cm mass with lymphovascular invasion, necrosis and mitosis	NED at 13 months	
5		M/ 88/parotid	1 years	Poorly circumscribed 4 cm mass with nuclear pleomorphism and moderate mitosis	Died at 5 years from unrelated causes	
6	Akhtar et al. [34]	M/80/left parotid	1 month	2.5 × 2.0 × 2.0 unencapsulated tumour with nuclear hyperchromasia, several mitosis and sebaceous differentiation	Follow up unavailable	Not known
7	Shulman et al. [35]	F/68/right parotid	8 years	8 cm nodule with lobules of vacuolated tumour cells with infrequent mitosis	Recurrence at 1 year	Not known
8	Siriwardena et al. [36]	F/57/right parotid	8- 9 months	Well circumscribed 2 × 1.5 × 1.0 mass pleomorphism and mitosis	Follow up unavailable	Not known
9	Silver et al. [37]	F/22/right parotid	1 month	6 × 4.5 × 3.5 cm cystic rubbery mass with cells composed of vacuolated cytoplasm	NED at 2 years	Not Known
10	Mc Farlane et al. [38]	F/74/left parotid	4 years	Circumscribed unencapsulated ovoid mass with nodular aggregates of large cells with hyperchromasia and mitosis	NED at 3 years	None
11		F/76/right parotid	6 years		NED at 1 years	
12	Grieve et al. [39]	F/73/left parotid	1 year	Lobulated unencapsulated 4 × 3.5 × 3.0 cm mass with numerous mitosis, hemorrhage and necrosis	NED at 6 months	Not known
13	Warman et al. [40]	M/83/right parotid	4 months	Lobulated neoplasm composed of basaloid, sebaceous and squamous differentiation	Died 1 year postoperative	None
14	Das et al. [41]	M/51/right parotid	9 months	Lobulated neoplasm 3.5 × 2.5 × 2.0 cm showing sebaceous differentiation. Mitosis was seen (7/10HPF)	NED at 6 months	Not Known
15	Mighell et al. [42]	F/87/left parotid	3 weeks	Lobular pattern of neoplasm with sebaceous differentiation	NED at 6 months	None
16	Takada et al. [43]	M/75/M/ left parotid	1 years	3 cm lobulated tumour composed of cells with sebaceous differentiation with prominent nucleoli and mitosis	NED at 7 months	None
17	Alexander et al. [44]	M/57/right parotid	10 months	Unencapsulated circumscribed 2.5 × 2.3 × 1.8 cm mass with necrosis, mitosis (2–4/hpf)	NED at 6 months	Not known
18	Tsukade et al.	M/ 70/parotid	–	Small area of mixed tumour, weakly mucicarminophilic material in stroma	Two recurrences	Not known
19	Foote et al. [34]	–/–/parotid	–	? Antecedent mixed tumour	–	Not known
20	Cheek et al. [34]	M/ 29/parotid	–	Well defined minor mucin producing component	NED at 3 years	Not known
21	Evans and Cruickshank et al. [34]	F/ 58/parotid	–	Infiltrating tumour, antecedent mixed tumour	Follow up unavailable	Not known
22		F89/parotid	–	Infiltrating sebaceous element. Some areas of mucin production. Antecedent mixed tumour or mucoepidermoid carcinoma or both	Follow up unavailable	Not known
23	Constant et al. [34]	F/ 61/parotid	–	Infiltrating carcinoma. No special stains reported	Died 2 years postoperative	Not known

Table 1 continued

No	Author	Sex/age/ location	Duration of symptom	Pathology	Follow up	Associated tumours
24	Takata et al. [45]	M/50/right parotid	1 year	22 × 15 × 10 mm solid infiltrating tumour with pleomorphism and atypical mitosis	Died of cerebral metastasis 13 months after resection	Not known

NED no evidence of disease

DNA mismatch repair protein leading to microsatellite instability [46]. Muir Torre Syndrome refers to *an* independent description made by Muir and Torre more than 4 decades ago about sebaceous carcinoma occurring *in association* with an internal malignancy [1, 2]. The most common malignancies occurring *in this* disorder, in decreasing frequencies include colorectal (80 %), endometrial cancers (20–60 %), stomach (11–19 %), urinary tract (4–5 %) along with sebaceous neoplasms of the skin [47].

The patient *herein* described had periampullary/pancreatic adenocarcinoma in 1994, colonic adenocarcinoma in 1995, gastric carcinoma in 2003, multiple cutaneous sebaceous adenomas over a period of approximately 20 years, 3 cutaneous squamous cell carcinomas and one sebaceous carcinoma of the scalp before developing a sebaceous carcinoma in her left parotid gland in 2015.

We were unable to retrieve the exact date when the diagnosis of Muir Torre Syndrome was made. *Due to the expense we did not repeat the mutational analysis for MSH2 and MLH1.* Bearing in mind that the inheritance of a defective gene encoding a DNA mismatch repair protein leads to a loss of the wild type allele with genomic microsatellites instability (MSI) and lack of protein expression, we used the mismatch repair protein expression on immunohistochemistry put forward by Mathiak et al. as a surrogate for genetic expression [48].

Most of the tumour cells showed negative nuclear staining for mismatch repair protein MSH2 supportive of a mutation in the gene (Fig. 7a) and positive nuclear staining for MLH1 (Fig. 7b).

It is beyond the purpose of this study to have an in depth discussion about the underlying genetics of MTS as our aim is to report the association between parotid sebaceous carcinoma in Muir Torre Syndrome [18–29] which, to the best of our knowledge has not been described *to date*.

We reviewed the literature and were able to retrieve 24 out of 29 *reported* cases of parotid sebaceous carcinoma. We were unable to review 5 cases despite extensive search (Table 1).

We believe the sebaceous carcinoma in this case was detected at an early stage because the patient was under

(a)

(b)

Fig. 7 a, b Immunohistochemistry in parotid gland sebaceous carcinoma for MSH2 shows negative staining in tumour cells and positive staining in lymphocytes and normal salivary gland confirming the MSH2 microsatellite instability. **b** Non mutated MLH1 in parotid gland sebaceous carcinoma. Immunohistochemistry shows positive staining in tumour cells and normal salivary gland

regular follow up for her Lynch Syndrome. There was no perineural infiltration, which is reported in approximately 20 % of the cases [25, 26] and no vascular invasion was seen but this is extremely rare [25–30].

In the differential diagnosis we included sebaceous adenomas, mucoepidermoid carcinoma and *other* tumours of salivary glands showing sebaceous differentiation. The presence of lymphoid cells raises the possibility of sebaceous lymphadenoma, sebaceous lymphadenocarcinoma and Warthin's Tumour among the differential diagnosis. The lymphocytic infiltrate was very focal and most of the interface between the tumour and normal parotid gland was composed of fibrous tissue as shown in Fig. 3b, ruling out the possibility of sebaceous lymphadenoma and sebaceous lymphadenocarcinoma. Despite the cytology diagnosis, Warthin's Tumour was excluded because papillae lined by oncocytic cells or dense lymphoid infiltrate were not found. Sebaceous adenoma was excluded because of the cytological atypia which is not a feature of an adenoma. The lack of lymphoid tissue did not support a diagnosis of lymphadenoma. Similarly mucoepidermoid carcinoma was excluded because there were no mucous secreting cells on PAS-D staining.

The possibility of parotid metastasis from one of the cutaneous *carcinomas* was also taken into account especially from the head and neck area considering the unique lymphatic drainage of the parotid gland. There are two groups of lymphatics, one embedded in the substance of the gland and other group of subparotid glands lying in the lateral wall of pharynx. Their afferent vessels drain the root of nose, eyelids, the frontotemporal region, the external acoustic meatus, posterior part of palate, and floor of nasal cavity [49]. In this case the patient had three keratinising squamous cell carcinomas of the skin from right sternum, right frontal area, and upper lip and one sebaceous carcinoma from scalp. The absence of keratinisation in the left parotid carcinoma along with right side of two (right sternum, and right frontal area) squamous cell carcinomas ruled out a metastasis. The carcinoma of the upper lip was 2.9 mm thick removed in 2006. It was considered unlikely to metastasize after 9 years. To exclude a metastasis from the sebaceous carcinoma of the scalp, we reviewed the literature to find out the incidence of metastasis in non-ocular sebaceous carcinoma of skin. In a large review (1836 cases), Tryggvason et al. [50] found an association between tumour size and development of metastasis. The highest metastatic potential (33.3 %) was seen with tumour >5 cm, followed by tumours between 3 and 5 cm (17 %) and only 1.4 % when the tumour was less than 1 cm. The same study also showed that lymph node metastases developed within 4 years after the primary tumour was resected.

In the present case the scalp tumour was 3.2 mm which is well below 1.0 cm. Also the parotid sebaceous carcinoma developed >4 years after the scalp tumour was biopsied making the possibility of metastases very unlikely.

Conclusion

This is the first reported association of sebaceous carcinoma of parotid gland with Muir Torre Syndrome. In the differential diagnosis, multiple tumours of the salivary gland have been discussed. We believe that a diagnosis of sebaceous carcinoma of salivary gland may be the first presenting symptom of Muir Torre Syndrome.

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