RECURRENT MUCINOUS CARCINOMA OF SKIN MIMICKING PRIMARY MUCINOUS CARCINOMA OF PAROTID GLAND: A DIAGNOSTIC PITFALL

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Summary

A case of a 63-year-old man with a swelling lasting 2 years in the left infraauricular area is reported. Examination by fine needle aspiration cytology raised suspicion of mucoepidermoid or adenoid cystic carcinoma of the parotid gland and an excision was recommended. The lateral parotidectomy specimen showed a poorly circumscribed gelatinous tumor measuring 15 mm in diameter within the parotid gland tissue. Microscopically, the lesion featured large pools of mucin containing clusters of tumor cells with little atypia and low mitotic activity. Immunohistochemically, the tumor cells showed expression of epithelial markers and of both estrogen and progesterone receptors. Left lateral neck dissection revealed massive lymphogenous dissemination of the tumor. Retrospective analysis of a skin biopsy from the same anatomic area performed 8 years prior to parotid neoplasm displayed a tumor with identical microscopic appearance and immunohistochemical profile (additionally performed) which was, however, misdiagnosed as a benign lesion. The diagnosis of recurrent primary mucinous carcinoma of the skin infiltrating the parotid gland was established. The patient underwent radiotherapy and has been 3 years free of disease. The differential diagnostics of this rare tumor is discussed.

Key words: skin – salivary gland – mucinous carcinoma – FNAC

Souhrn

Recidiva mucinózního karcinomu kůže napodobující primární mucinózní karcinom příušní slinné žlázy: popis diagnosticky obtížného případu

Autoři popisují případ 63letého muže s dvouletou anamnézou zduření v levé infraaurikulární krajině. Při vyšetření pomocí tenkojehlové aspirační cytologie bylo vysloveno podezření na mukoepidermoidní či adenoidně cystický karcinom příušní slinné žlázy a bylo doporučeno chirurgické odstranění afekce. Ve vzorku z laterální parotidektomie byl zastižen neostře ohraničený hlenovitý nádor největšího rozměru 15 mm. Mikroskopicky nádor sestával z velkého množství hlenu, ve kterém byly přítomny skupinky nádorových buněk bez výraznějších atypií s nízkou mitotickou aktivitou. Imunohistochemicky nádorové buňky exprimovaly epiteliální markery a estrogenové a progesteronové receptory. Následně provedená levostranná krční disekce prokázala masivní metastatické postižení lymfatických uzlin. Při revizi kožní biopsie z téže anatomické krajiny provedené před 8 lety byl zastižen nádor identického mikroskopického vzhledu a imunohistochemického profilu (vyšetření bylo provedeno dodatečně), který byl ovšem chybně diagnostikován jako benigní afekce. Na základě výše uvedených nálezů byla stanovena diagnóza recidivy primárního mucinózního karcinomu kůže infiltrujícího příušní slinnou žlázu. Ve sdělení je diskutována diferenciální diagnostika tohoto vzácného nádoru.

Klíčová slova: kůže – slinná žláza – mucinózní karcinom – tenkojehlová aspirační cytologie

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Primary cutaneous mucinous carcinoma (CMC) is a rare neoplasm occuring mostly in middle-aged and elderly patients with slight male predominance (16). Although it may appear anywhere in the skin, the most common location is head, in particular the scalp and eyelids (16). Microscopically, CMC is characterized by large pools of mucin with clusters of tumor cells. Thus, its appearance makes CMC almost indistinguishable from primary mucinous carcinomas (MCs) of the salivary and lacrimal glands and from skin metastases of MCs from distant primaries, e.g. breast, gastrointestinal tract and ovaries. Although immunohistochemistry may be of some help in the differential diagnosis, in certain cases clinicopathological correlation including imaging methods is necessary.

We present a case of late recurrent CMC mimicking primary MC of the parotid gland, which appeared as a great diagnostic pitfall.

CASE REPORT

A 63-year-old man presented with a painless lesion in the left infraauricular area lasting for 2 years. Clinical examination showed a circumscribed nodule measuring 30 mm. Ultrasound examination revealed a nonhomogenous hypoechogenic mass measuring 22x20 mm in the parotid gland; no suspicious tumorous foci were detected in other organs, including the breasts and axillary lymph nodes. Examination by fine needle aspiration cytology (FNAC) was followed by left lateral parotidectomy with subsequent total left parotidectomy and left neck lymph node dissection. The patient underwent radiotherapy. He is free of disease for 3 years since the last operation.

A revision of the patient's history revealed excision of an "atheroma" in the same anatomic area 8 years ago.

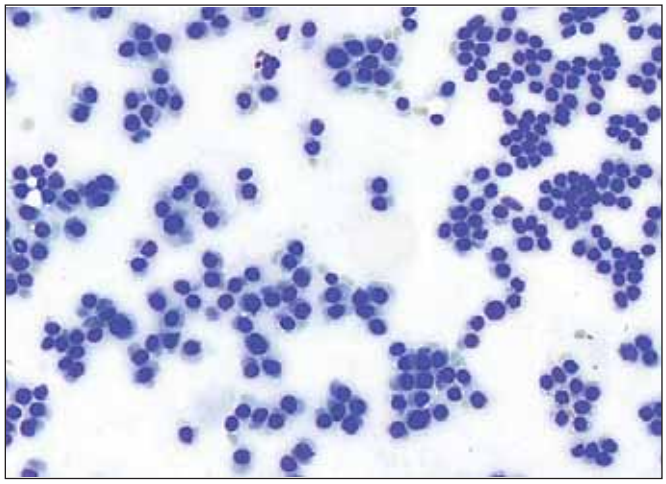

Fig. 1. Highly cellular smear shows clusters of monotonous tumor cells with round to oval nuclei and bluish cytoplasm with slightly increased nucleocytoplasmic ratio (May-Grünwald-Giemsa, original magnification 200x)

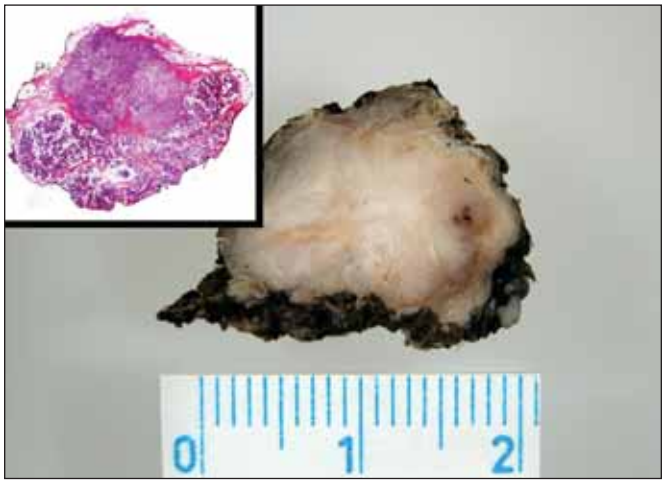

Fig. 2. The tumor was poorly circumscribed and featured solid gelatinous grey-white cut surface. Inset: The tumor infiltrated fat tissue of subcutis and parotid gland parenchyma (HE, original magnification 40x)

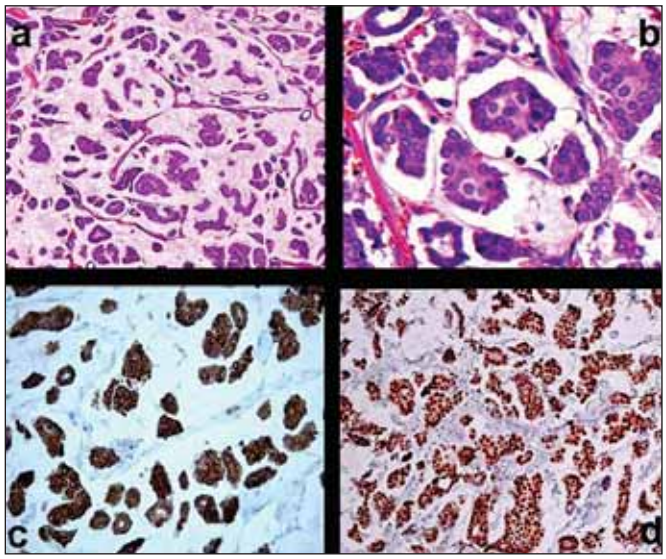

Fig. 3. a) Clusters of tumor cells in a mucinous background (HE, original magnification 200x). b) Tumor islets consist mainly of deeply eosinophilic cells with occasional pale cells in the central parts of nests (HE, original magnification 400x). c) Diffuse expression of cytokeratin 7 in tumor cells (original magnification 200x). d) Diffuse nuclear expression of estrogen receptor in tumor cells (original magnification 200x)

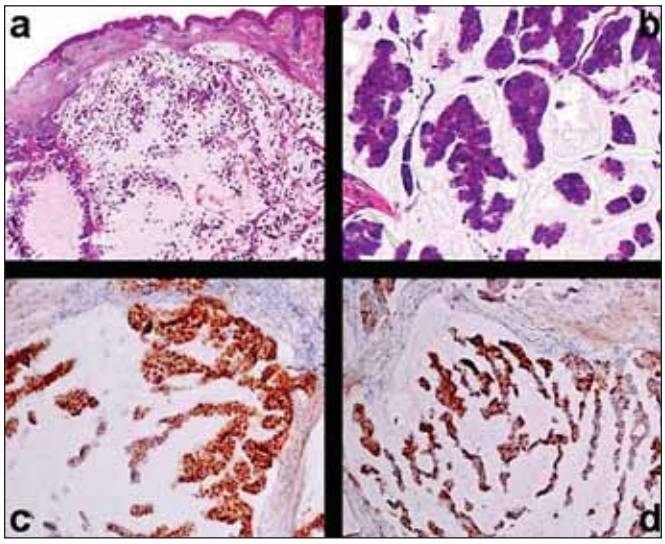

Fig. 4. a) Large mucinous tumor infiltrated dermis (HE, original magnification 40x). b) Tumor featured cell islets in a mucinous stroma similar to those in Fig. 3b (HE, original magnification 200x). c) Diffuse nuclear expression of estrogen receptor (original magnification 200x). d) Diffuse nuclear expression of progesterone receptor (original magnification 200x)

MATERIALS AND METHODS

The air-dried FNAC smears were stained with May-Grünwald-Giemsa.

The tissue specimens were immediately fixed in formalin, embedded in paraffin and routinely processed. Indirect immunohistochemistry using monoclonal antibodies against cytokeratins (CK) (clone AE1/AE3, dilution 1:50), CK7 (OV-TL 12/30, 1:50), CK20 (Ks 20.8, 1: 25), epithelial membrane antigen (EMA) (NCH-38, 1:800), carcinoembryonic antigen (CEA) (II-7, 1:800), S-100 protein (S100) (4C4.9, 1:3,000), smooth muscle actin (SMA) (1A4, 1:200), p63 protein (p63) (4A4, 1:200), calponin (CALP[1], 1:500), estrogen receptor (ER) (1D5, 1:50), progesterone receptor (PR) (PgR636, 1:300), p53 protein (p53) (DO-7, 1:300) and Ki-67 (MIB-1, 1:50) was performed. The source of S100 was NeoMarkers (Fremont, USA), the source of all remaining antibodies was Dako (Glostrup, Denmark). Antigen retrieval was performed in a water bath for 40 minutes at 97C in the target retrieval buffers at different pH values – at pH 6.0 (buffer S1700) for CK, CK20, calponin, CEA, S100, and at pH 9.0 (buffer S2367) for ER, PR, p53 and Ki-67. For CK7 and p63, the tissue was processed in the microwave vacuum histoprocessor RHS 1 (Milestone) at pH 6.0 at 120C for 4 minutes. Endogenous peroxidase activity was inhibited by immersing the sections in 3% hydrogene peroxide. Finally, the sections were incubated with EnVision+ Dual Link System-HRP (Dako). The reaction was visualized using diaminobenzidine. In addition, the detection of Her-2/neu protein expression was performed using certified HercepTest assay according to the instructions of the manufacturer (Dako).

RESULTS

The FNAC smears showed highly cellular aspirates of uniform cells with round to oval nuclei and vacuolated light blue cytoplasm with increased nucleocytoplasmic ratio on a bluish mucinous backgroud (Fig. 1). This finding was interpreted as suspicious of mucoepidermoid or adenoid cystic carcinoma of parotid gland and surgery was recommended.

The lateral parotidectomy specimen measured 45x30x25 mm and showed a poorly circumscribed tumor measuring 15 mm in its greatest diameter with grey-white gelatinous cut surface (Fig. 2).

Microscopically, an uncapsulated tumor infiltrating subcutaneous fat and the parotid parenchyma was found (Fig. 2, inset). The tumor stroma contained large pools of mucin showing positive staining with alcian blue and colloidal iron; it was also PAS positive both without and with diastase pretreatment. Solid, micropapillary and tubular clusters of slightly polymorphous round to oval tumor cells featuring oval nuclei with distinct nucleoli and abundant deeply eosinophilic cytoplasm were present in the mucinous stroma, which was separated by delicate fibrous septa (Fig. 3a). Occasional cells with paler cytoplasm were present as well (Fig. 3b). The mitotic activity was generally low (max. 1-2/10 HPF); no atypical mitoses were found.

Immunohistochemically, the tumor cells showed diffuse expression of CK, CK7 (Fig. 3c), EMA and focal positivity of CEA. In addition, the tumor cells featured strong nuclear expression of both ER (Fig. 3d) and PR. Immunohistochemical detection of CK20, S100, SMA, p63 and Her-2/neu protein was negative. Oncoprotein p53 was positive in isolated cells; proliferation marker Ki-67 was positive in about 10% of tumor cells.

The tumor tissue was found in the deep lobe of parotid gland in the specimen from total parotidectomy and, in addition, 16/17 of neck lymph nodes showed metastatic involvement.

Retrospective analysis of the skin biopsy excised 8 years ago, which had been misdiagnosed as a benign adnexal skin tumor, revealed a large tumor in the dermis showing similar microscopic appearance (Fig. 4a, 4b) and immunohistochemical profile (performed additionally), including ER (Fig. 4c) and PR (Fig. 4d) expression. The oncoprotein p53 was positive in 5% of tumor cells; the proliferation marker Ki-67 was positive in about 20% of tumor cells. No *in situ* component of the tumor was found, even when immunohistochemical detection of p63 and calponin expression was used. The surgical margins were positive.

The diagnosis of recurrent cutaneous MC infiltrating the parotid gland with massive lymphogenous dissemination was established.

DISCUSSION

Primary cutaneous mucinous carcinoma (CMC) is a rare adnexal neoplasm with approximately 150 cases reported in the literature since its first description by Lennox et al. in 1952 (17). Most cases are published as case reports (3, 4, 6–8, 15, 20, 28); rarely, larger series have been reported (14, 26). Although its precise histogenesis has still not been elucidated (19), there is some evidence supporting an apocrine nature of this tumor (27) arising from *in situ* lesions (14).

CMC mostly occurs in middle-aged and elderly patients with slight male predominance and usually presents as a solitary asymptomatic raised mass of varying color ranging from 1 to 8 cm in size (16). Although about 75% of cases occur on the scalp and face (with predilection for lower eyelid), the tumor may also appear on the cheek, nose and chin (16); rare involvement of the abdomen (26), axilla (1), vulva (22), groin (9) and foot (10) has been also reported.

Microscopically, CMC demonstrates large pools of basophilic mucin separated by thin fibrous septa containing islets or clusters of tumor cells arranged in a solid, micropapillary, tubular and/or cribriform pattern (16). The tumor cells feature slightly enlarged nuclei with distinct nucleoli and abundant cytoplasm which may be deeply eosinophilic or pale. While the dark cells are located mainly at the periphery of tumor nests and are responsible for production of mucin, the pale cells tend to be located more centrally and are thought to be stem cells that differentiate into the dark cells (21). As a rule, the tumor cells show little atypia and low mitotic activity. The mucinous material features histochemical characteristics of sialomucin of epithelial origin (16). Very rarely, CMC may show focal neuroendocrine differentiation (5, 29).

Immunohistochemically, tumor cells show constant expression of CK, EMA and CEA; S100 staining is more variable. Interestingly, there is strong nuclear expression of ER, while PR detection may give variable results (11).

There are only sporadic reports (23, 24) dealing with FNAC characteristics of CMC showing similar findings with the herein presented case, i.e. moderately to highly cellular smears consisting of lakes of mucin with clusters of monotonous bland-looking epithelial cells.

On histology, the differential diagnosis of CMC is mainly with primary MCs of salivary glands (incl. mucin-rich variant of salivary duct carcinoma (M-SDC))(18), lacrimal glands, nose and paranasal sinuses, and with skin metastases of MCs of breast, bronchi, ovaries, prostate and renal pelvis. Primary MCs of salivary glands tend to occur in minor salivary glands and, similarly with MCs of lacrimal glands, nose and paranasal sinuses, they are ER/PR negative (12). The misdiagnosis may be, however, of little clinical significance since primary MC of salivary glands, similarly like CMC, tends to recur locally and has a propensity for lymph node metastases (2). On the other hand, M-SDC is a highly aggressive malignant tumor, displaying atypical polymorphous neoplastic cells with high mitotic activity and ER/PR-negative and androgen receptor-positive profile with variable Her-2/neu protein expression on immunohistochemistry (25).

Distinguishing between CMC and skin metastases of visceral MCs may be very difficult (14). In general, skin metastases tend to occur in advanced stages of diasease, tend to be topographically related, i.e. MC of bowel tends to infiltrate skin of abdomen, tend to show pronounced cytologic atypia and less mucin and lack the *in situ* component. MCs of bronchi, prostate, renal pelvis and gastrointestinal tract are ER/PR negative and may show expression of other markers which are not expressed in CMC, e.g. thyroid transcription factor 1, prostatic specific antigen, and CK20. Since both MC and micropapillary carcinoma of breast and MC of ovaries show ER/PR expression, clinicopathological correlation including imaging methods is necessary. Finally, malignant mixed tumor of the skin features no separating fibrous septa in the mucoid/myxoid stroma and is ER/PR negative (16).

CMC behaves as a low-grade malignant neoplasm which is prone to local recurrence in about 30% of cases and to lymphogenous dissemination in about 10% of cases (21). Distant metastases occur much less frequently in about 3% of cases (13). Since CMC tends to be chemo- and radioresistant, surgical resection with sufficient margins is an optimal treatment (16).

In summary, we present a case of late recurrent primary mucinous carcinoma of the skin which had been initially misdiagnosed as a benign skin tumor and which we have found a difficult diagnostic pitfall when dealing with its recurrence.

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