Heterotopic acinic cell carcinoma and its clinical implications

Ivo Starek*, Richard Salzman*, Alena Skalova

This is a review of the clinical and histopathological published data on very rare heterotopic acinic cell carcinomas (AcCCs) with suggested optimal management. Extrasalivary AcCCs originate primarily in parotid lymph nodes. They present at low clinical stage, show mostly low-grade histopathology and are circumscribed with a complete nodal capsule. Extracapsular dissection was advocated as adequate therapy. In rare cases with positive surgical margins, a completion parotidectomy or adjuvant radiotherapy should follow. Heterotopic high-grade AcCCs are rare, necessitating radical surgery including neck dissection and adjuvant radiotherapy. The short term prognosis is excellent, long term outcomes are not known. Longer term follow-up is essential.

Key words: acinic cell carcinoma, heterotopia, lymph node, salivary gland

INTRODUCTION

Heterotopic (ectopic) salivary tumours arise from neoplastic transformation of aberrant salivary tissue present outside the “orthotopic” major, minor and accessory salivary glands. Salivary heterotopias occur rarely in lymph nodes and extremely sporadically in various extranodal head and neck locations where they clinically appear as soft tissue masses. In cephalic positions, they are believed to be portions of salivary gland rudiments dislocated during embryonic development. Moreover, they can be found in anterior7 and exceptionally also in the posterior neck2, here presenting as a nontender swelling and/or scantily draining sinus. Cervical salivary heterotopias occurring near the sternoclavicular joint or those associated with branchiogenic and thyroglossal malformations are postulated to be heteroplasias of ectodermal remnants of the precervical sinus of His or thyroglossal duct. A similar mechanism seems to be involved in the development of heterotopic salivary tissue in the breast1, gastrointestinal4 and urogenital tract3.

The majority of salivary heterotopias occur in the parotid and suprahoid lymph nodes. They are composed of intercalated, striated or intralobular ducts, serous acini may be present occasionally2. Intranodal location of salivary tissue, as well as the presence of lymph nodes in the parotid, can be explained by the intermingling of salivary primordia and condensing mesenchyma of the second branchial arch occurring in the 7th embryonal week. Brown7 found salivary tissue in intraparotid lymph nodes in all of 19 autopsied newborns. In some adults, the heterotopic intranodal salivary tissue persists and may clinically mimic a tumour due to various histological changes of the epithelium8.

Generally, except for Warthin tumour, extrasalivary sialomas are extremely rare lesions. Seifert1 in a series comprising 6686 salivary gland tumours, found only three cases arising in intraparotid lymph nodes. Similarly, Warnock10 and Daniel11 reported solely 8 and 7 analogous cases, respectively, during a 25-year period.

In the histopathologic spectrum of heterotopic intranodal sialomas benign lesions prevail. Among them, Warthin’s tumour is the predominant entity, followed by much less frequent pleomorphic adenoma12-13. In the malignant group, the commonest tumours are high- and low-risk mucoepidermoid carcinomas and acinic cell carcinomas (AcCCs), other entities (such as oncocytic carcinoma, sialoblastoma, salivary duct carcinoma, adenoid cystic carcinoma, myoepithelial carcinoma) occur sporadically9,11,13-20.

Intranodal occurrence of a salivary carcinoma which is not associated with a tumour arising from an “orthotopic” salivary gland raises a question whether it represents a heterotopic or metastatic lesion from an unknown primary. An inappropriate decision jeopardizes the patient with treatment failure of the primary neoplasm or unnecessary surgery of an adjacent tumour free salivary gland with its associated morbidity. The solution to that dilemma is based on the three following criteria16-21: 1. no primary “orthotopic” carcinoma detected clinically or using relevant imaging methods. 2. microscopic evidence of glandular ductal and/or acinar inclusions in the affected lymph node. However, the absence of these structures does not exclude the diagnosis of an ectopic tumour, since they may be replaced by carcinoma cells. Besides, one must keep in mind that both events might at least theoretically, coincide. 3. the tumour must be completely embedded within nodal tissue which is sharply demarcated from...
the parenchyma of the “orthotopic” salivary gland. The primary intranodal origin of a salivary carcinoma is further supported by its predominant central growth which corresponds with occurrence of salivary inclusions in this location. In equivocal cases, a definite conclusion can be achieved solely by a long-term follow-up.

Intranodal origin of AcCC, both primary or metastatic, may be challenging in cases endowed with lymphoid stroma22 which is easily mistakable for a lymph node22. In these cases, evidence of residual anatomical structures of the latter (i.e. medular or subcapsular sinuses or a hilum) is usually critical.

Management of the “orthotopic” salivary carcinomas is specified in generally accepted guidelines NCCN (ref.24). However, the extreme rarity of heterotopic salivary carcinomas and the consequent absence of relevant data with resulting uncertainty in their biological character precludes implementation of therapeutic standards. Surgical procedures in heterotopic AcCCs which are being typically diagnosed postoperatively may vary from extensive to limited. The latter is occasionally followed by completing surgery and adjuvant radiotherapy.

In the current WHO classification, AcCC is categorized as a low-risk lesion Simpson25. However, individual cases may demonstrate a protracted, unpredictable and potentially fatal clinical course. Therefore, clinicopathologic features, therapeutic strategies and prognosis of major and minor salivary gland AcCCs were quite recently reviewed in a comprehensive analysis consisting of 156 reference26. We believe that the results should be adopted for the heterotopic variant of this carcinoma, enabling thus optimal individual treatment.

RESULTS

Our literature research identified only 18 cases of heterotopic AcCCs. Four of them, reported by Abrams27 and Evans28 were not properly described. Sufficient data were available in other 14 patients (including our one) presented by 10 independent authors9,11,16,21,29-34 (see Table 1).

Except for a carcinoma originating presumably from aberrant extranodal salivary tissue of the upper neck (pt. 12), all other 13 tumours arose from low- or mid-cervical (pts. 1, 4 and 6), intra- (pts. 2, 8, 9, 10, 11, 13 and 14) and paraparotid intranodal (pts. 3, 5 and 7) salivary heterotopias. In 12 patients in whom gender was known, a considerable (10 to 2) female preponderance was noticed. The age varied from 7 to 62 (mean 36.9) years. The size of particular tumours that was available in 9 cases did not exceed 3.5 cm, seven of which were less than 3 cm. Six of seven carcinomas were mobile, in the other seven cases, no relevant information was provided. In pt. 4 local findings was suspicious of malignancy.

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Relevant treatment data were available in all but one (pt. 9) patient. Nine intra/paraparotid intranodal tumours were treated using a simple excision alone (pts. 1, 12 and 14) or in combination with adjuvant radiotherapy (pt. 2, 7) or a superficial/partial parotidectomy without (pts. 3, 5, 8, and 13) or with neck dissection (pts. 10, 11). The latter procedure was subsequently followed by a completion parotidectomy (pt. 13). In three of four patients with carcinomas located in the upper or lower neck, simple resection alone (pts. 1 and 12) or completed with superficial parotidectomy (pt. 6) was performed. In the pt. 4, the treatment consisted of comprehensive neck dissection, superficial parotidectomy and resection of the submandibular gland. All patients presented as cN0. The histopathologic nodal status could be evaluated only in 5 patients after a neck dissection (pts. 4, 10 and 11) or nodal excision (pt. 3 and 8). A metastasis was demonstrated

Table 1. Previously reported cases of heterotopic acinic cell carcinoma.

<table>
<thead>
<tr>
<th>No.</th>
<th>author</th>
<th>Sex, age (y)</th>
<th>Loc.</th>
<th>Size (cm)</th>
<th>Mobility</th>
<th>Therapy</th>
<th>f-up (mo)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Bhaskar</td>
<td>M, 17</td>
<td>IN, LN</td>
<td>NA</td>
<td>NA</td>
<td>E</td>
<td>NA</td>
<td>29</td>
</tr>
<tr>
<td>2.</td>
<td>Kleinsasser</td>
<td>F, 47</td>
<td>IN, IP</td>
<td>chestnut</td>
<td>semifixed</td>
<td>E+RT</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>3.</td>
<td>Perzin</td>
<td>F, 18</td>
<td>IN, PP</td>
<td>3.5 cm</td>
<td>mobile</td>
<td>ParP</td>
<td>12, NED</td>
<td>21</td>
</tr>
<tr>
<td>4.</td>
<td>Perzin</td>
<td>F, 66</td>
<td>IN, MN</td>
<td>2.5 cm</td>
<td>NA</td>
<td>SP+ND+SGE</td>
<td>12, fem. meta</td>
<td>49</td>
</tr>
<tr>
<td>5.</td>
<td>Yacoub</td>
<td>F, 7</td>
<td>IN, PP</td>
<td>2 cm</td>
<td>mobile</td>
<td>SP</td>
<td>12, NED</td>
<td>31</td>
</tr>
<tr>
<td>6.</td>
<td>Zajtchuk</td>
<td>M, 10</td>
<td>IN, LN</td>
<td>NA</td>
<td>NA</td>
<td>E+SPE</td>
<td>45, NED</td>
<td>16</td>
</tr>
<tr>
<td>7.</td>
<td>Zajtchuk</td>
<td>F, 47</td>
<td>IN, PP</td>
<td>NA</td>
<td>NA</td>
<td>E+RT</td>
<td>10, NED</td>
<td>16</td>
</tr>
<tr>
<td>8.</td>
<td>Minic</td>
<td>F, 37</td>
<td>IN, IP</td>
<td>2.5 cm</td>
<td>mobile</td>
<td>SP</td>
<td>20, NED</td>
<td>32</td>
</tr>
<tr>
<td>9.</td>
<td>Seifert</td>
<td>F, 62</td>
<td>IN, IP</td>
<td>1.6 cm</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>9</td>
</tr>
<tr>
<td>10.</td>
<td>Daniel</td>
<td>NA</td>
<td>IN, IP</td>
<td>NA</td>
<td>NA</td>
<td>SP+ND (N0)</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>11.</td>
<td>Daniel</td>
<td>NA</td>
<td>IN, IP</td>
<td>NA</td>
<td>NA</td>
<td>SP+ND (N0)</td>
<td>24, NED</td>
<td>11</td>
</tr>
<tr>
<td>12.</td>
<td>Das</td>
<td>F, 32</td>
<td>ExN, UN</td>
<td>1.5 cm</td>
<td>mobile</td>
<td>E</td>
<td>NA</td>
<td>33</td>
</tr>
<tr>
<td>13.</td>
<td>Alsayeg</td>
<td>F, 38</td>
<td>IN, IP</td>
<td>2 cm</td>
<td>mobile</td>
<td>SP+TP</td>
<td>NA</td>
<td>34</td>
</tr>
<tr>
<td>14.</td>
<td>our patient</td>
<td>F, 62</td>
<td>IN, PP</td>
<td>1.3 cm</td>
<td>mobile</td>
<td>E</td>
<td>24, NED</td>
<td></td>
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</tbody>
</table>

PP paraparotid, IP intraparotid, IN intranodal, ExN extranodal, LN lower neck, UN upper neck, MN middle neck, EN encapsulated, SM surgical margins, E excision, SP superficial parotidectomy, TP total parotidectomy, ND neck dissection, SGE submandibular gland excision, ParP partial parotidectomy, NA not available
only in the patient No. 4, in whom the tumour showed foci of dedifferentiation. Information on the quality of the nodal capsule was available in 6 patients. In four of them (pts. 2, 5, 8, 9), the capsules were tumour-free. A slight capsular invasion was present only in the pt. 13 and in the pt. 14, the capsule was focally absent (Fig. 1). In all cases, in which parotidectomy specimens were obtained, the overlying parotid tissue was free of carcinoma (pts. 3, 8, 5, 9, 13). Aberrant intranodal salivary inclusions were seen only in pts. 8, 13 and 14 (Fig. 1).

Follow-up ranging from one 10 to 45 (mean 19.9) months was obtained in eight atients. All were alive and excluding the patient 4, with no evidence of disease.

As far as it can be assessed from histopathologic descriptions of particular cases, the majority of them showed a histopathologic pattern of a conventional low-grade AcCC, areas of dedifferentiation were present solely in the patient pt. 4.

DISCUSSION

AcCC accounts for about 11% of all salivary malignancies. About 90% of cases originate from the parotid and the remaining from other major and minor, primarily buccal and upper lip glands Biron. With a slight female prevalence, the AcCCs are evenly distributed throughout all decades with the proclivity to occur at a younger age than other salivary gland carcinomas. Children are affected very rarely. AcCCs are diagnosed mostly at initial clinical stages. The presented review demonstrates that the sex and age distributions of heterotopic AcCCs meet those arising in the parotid. Moreover, like the majority of “orthotopic” AcCCs, they are asymptomatic, freely mobile, not sizable, and slowly progressing lesions.

Although considered to be the most favourable among all salivary gland carcinomas, AcCC must not be labelled innocent. Prior institutional studies mentioned the 5, 10 and 15-year survival rates to reach about 83%, 76% and 65%, respectively Spiro. However, the results might have been distorted by referral/selection bias. A recent population-based study is more optimistic, indicating 97%, 94% and 90% overall survival at 5, 15 and 20 years, respectively Patel.

Vagarity in the clinical course of AcCCs had initiated attempts at identification of prognostic factors, applicable in its management. A large multivariate analysis was performed elaborating data of a total of 3345 AcCC patients collected by three independent institutions. In this analysis, increasing age, male gender, non-caucasian race, minor salivary gland origin, positive resection margins, inadequate previous treatment, irradical resection, TNM parameters, proliferative activity, and tumour grade proved to be adverse factors.

Histopathological grading of AcCC has not been suggested in the current WHO classification of salivary gland tumours. Nonetheless, its prognostic relevance was recently confirmed by Gomez demonstrating the 5-year disease-free/overall survival rates to be 94/100% and 54/69% for low- and high-grade tumours, respectively. Prognosis in patients diagnosed with AcCCs largely deteriorates with the occurrence of high-grade transformation.

Fig. 1. Heterotopic intranodal AcCC showing a solid-microcystic pattern (triangles) in patient 14. The nodal lymphoid tissue (asterisk) is pushed to the tumour periphery covered with a thin rim of fibrous tissue with two intranodal salivary inclusions represented by dilated duct (arrows). (H.E.)
These cases are significantly associated with lymph node and distant metastasis with about two-thirds of them dying from the disease after a median of 4.3 years Skalova42.

All but one analyzed patients were alive and disease-free. The only exception was the patient with dedifferentiated AcCC who had developed a femoral metastasis and may have died of the tumour. However, the follow-up of particular cases was too short, not covering the potentially very prolonged and fatal course, known in the parotid AcCCs. The time patients with these neoplasms should be followed-up, necessitates at least ten years41. The long-term prognosis of ectopic AcCCs thus remains unclear. It is not clear whether it equals that of the parotid or minor salivary gland AcCCs. The prognosis of the latter group was reported to be less favourable, i.e. 25-year survival rate and incidence of metastasis making 50 and 20%, respectively43. The worse outcome is related to the preponderance of high grade pathology43 and common infiltrative growth44. Moreover, some adverse anatomic locations and invariably lacking capsule increase the risk of incomplete resection of minor salivary AcCCs.

Rational treatment of salivary carcinomas is a complete resection aiming at achieving tumour-free margins. On account of inconsistent encapsulation and occasional extracapsular extensions, the AcCCs must be removed (as well as all other low-risk salivary carcinomas) along with a rim of a tumour-free surrounding tissue. For those originating from the parotid, superficial or total parotidectomy dependently from the stage and tumour location (superficial vs. deep parotid lobe), are usually preferred40,42. However, in benign looking low-stage/low-gra

We could find only a single case of extranodal heterotopic AC with unavailable information on the capsule quality. We can but speculate that this would be analogous to that in the major or small salivary gland AcCCs, i.e. incomplete or even absent, necessitating thus resection with a generous rim of adjacent tissue. Because of extreme scarcity, the extranodal heterotopic AcCCs are usually not taken into differential diagnostic considerations of neck masses. Consequently, the surgery would most probably have explorative character, hardly reaching negative resection margins. However, cervical location of extranodal heterotopic AcCCs makes a revision surgery easy, not associated with significant postoperative morbidity.

In the current analysis, only the patient with dedifferentiated AcCC showed multiple nodal metastasis, all others were staged as N0. The low lymphangiogenous spread accords well with the reported merely 10% incidence of nodal involvement in “orthotopic” AcCCs which is usually associated with high-grade features and/or advanced T stage43. An elective neck dissection is, thus, not recommended in the extrasalivary AcCCs, unless they show the latter two characteristics.

In our review, two patients (2 and 7) received adjuvant radiotherapy after a simple resection of benign-looking intranodal heterotopic AcCC. Indications for the RT were not stated explicitly by the referring authors. On the other side, the patient (No. 4) with a dedifferentiated carcinoma revealing nodal metastases, received extensive surgery only and developed a femoral metastasis one year later. These cases illustrate ambiguity in the view on adjunctive radiotherapy in heterotopic AcCCs. That issue in “orthotopic” AcCCs was addressed largely by Vander Poorten et al.45. After a thorough and critical literature review, the author summarized that in analogy with other salivary gland carcinomas, additional radiotherapy should be given in cases with T3/T4 stages, high-grade histopathology, high proliferative index, regional lymphatic metastasis, positive surgical margins, perineural invasion and salvage surgery for tumour recurrence. The limited number of published heterotopic AcCCs and inadequate follow-ups preclude any solid guidelines regarding criteria for radiotherapy of these lesions. However, in our opinion, they should be analogous with those applied for the common AcCCs.

CONCLUSION

Extrasalivary AcCCs are very rare lesions. They originate mostly from intra- or paraparotid intranodal salivary heterotopias. Presenting as clinically benign lesions, they are diagnosed typically at low-clinical stage. Because of
prevalence of low-grade histopathology and node capsule at the periphery of intranodal AcCCs, the authors advocate extracapsular dissection as adequate therapy. With positive surgical margins, a completion parotidectomy or adjuvant radiotherapy should follow. Heterotopic high-grade AcCCs are rare, necessitating radical surgery including neck dissection and adjuvant radiotherapy. Short term prognosis of heterotopic intranodal AcCCs is generally excellent, long term outcomes are not known. Consequently, an adequate follow-up is essential.

Search strategy and selection criteria
The PubMed and Embase databases were searched with the Medical Subject Headings (key-words: acinic cell carcinoma, lymph node, salivary gland, heterotopia). A manual search of the bibliographic of relevant studies was also performed to identify additional papers. The date of publication and language were not restricting selection criteria. Only cases of AcCCs declared by particular authors to meet the above-mentioned criteria for heterotopic origin were included. Controversial may be considered one of the two patients reported by Perzin et al. In this case, an intranodal AcCC was found in the middle neck and metastatic cells were detected also in many adjacent lymph nodes. The resected ipsilateral submandibular gland and superficial parotid lobe were free of carcinoma. The authors speculated that a microscopic primary might have gone undetected in the deep parotid but stated that he was not aware of any occult AcCC to develop metastases. In another patient, a dedifferentiated AcCC was completely embedded in an intraparotid lymph node. However, a microscopic, supposedly primary carcinoma was found in the resected superficial parotid lobe. Ectopic origin of that tumour is, therefore, debatable and the case could not be accepted.

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REFERENCES
22. michal M, Skalová A., Simpson RH, Řyška A, Šárek I. Well differen-
27. Abrams AM, Corny J, Schoffield H, Hansen LS. Acinic cell adeno-