MUCOEPIDERMOID CARCINOMA OF SALIVARY GLANDS IN THE PEDIATRIC AGE GROUP: 18 CLINICAL CASES, INCLUDING 11 SECOND MALIGNANT NEOPLASMS

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Accepted 23 December 2005
Published online 16 June 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20429

Abstract: Background. Salivary gland tumors represent 1% of head and neck tumors, with only 5% of these occurring in patients younger than 20 years. Mucoepidermoid carcinoma (MEC) is one of the most frequent salivary gland cancers among adults and children.

Methods. This survey was conducted among 34 French pediatric oncology departments. From 1980 to 2000, 18 cases were reported.

Results. Treatment included surgery or radiotherapy, or both. The 5-year survival rate was 93.7%. Eleven patients had been previously treated by radiotherapy and/or chemotherapy for a first malignant tumor, specifically, lymphoid leukemia (n = 4), lymphoma (n = 3), brain tumor (n = 2), sarcoma (n = 1), and rhabdomyosarcoma (n = 1).

Conclusions. MEC is very rare in the pediatric age group. Treatment involves surgical removal of the tumor plus radiotherapy, according to histologic staging. MEC has a good prognosis in young patients. The survival rate does not differ in the subgroup of patients with MEC as a secondary tumor.

Keywords: salivary gland neoplasms; mucoepidermoid carcinoma; second primary neoplasms; child; adolescent

Salivary gland tumors (benign or malignant) represent only 1% of head and neck tumors; approximately 5% of these occur in children or adolescents. Most of these tumors are nonepithelial, such as hemangioma. Among epithelial tumors of the salivary glands, mucoepidermoid carcinoma
(MEC) and adenoid cystic carcinoma are the most frequent histologic types in adults and in children.

Our study is a descriptive, retrospective, and multicenter analysis of a series of 18 patients younger than 20 years who were treated for salivary gland MEC in French pediatric oncology departments from 1980 to 2000. The aim of this study was to define the diagnostic and therapeutic characteristics of MEC in children.

PATIENTS AND METHODS

We sent a questionnaire to the 34 French pediatric oncology departments. Among the 22 answers received, clinical, pathologic, and follow-up data were provided for 18 cases from 6 departments. When MEC occurred as a secondary cancer, the tumor and treatment characteristics for the original cancer were recorded. Tumors were staged according to the TNM classification of malignant tumors of the Union Internationale Contre le Cancer (UICC) from 1997; we used pathologic grading criteria established by Batsakis et al for MEC.

We defined the follow-up duration from the date of the end of treatment. Survival curves were calculated with use of the Kaplan–Meier method, and the relationships between the clinicopathologic variables and survival were assessed in univariate analysis using the log-rank test with Statview (SAS Institute, Cary, NC, USA) software.

RESULTS

Eighteen young patients (9 males and 9 females) with salivary gland MEC were reported from 1980 to 2002. The median age at diagnosis was 12 years (range, 4.0 to 19.5 years). Eleven patients had a history of a nonsalivary malignancy (Tables 1 and 2).

One patient was lost to follow-up after diagnosis, and 1 other patient rapidly died from primary medulloblastoma without any treatment for his parotid gland MEC. All 16 remaining patients had been treated with primary surgery: 2 superficial extrafacial parotidectomies; 10 total parotidectomies, with facial nerve resection in 3 cases; 2 submandibular gland resections, 1 extensive tonsillectomy; and 1 hard palate tumor excision. Intraoperative frozen-section analysis of the surgical specimen was performed in 6 cases, showing MEC only in 3 cases. Definitive pathologic diagnoses showed 11 low-grade, 3 intermediate-grade, and 2 high-grade salivary MECs. Neck lymph node metastasis, including 1 with extracapsular spread (ECS), was found in 4 of the 8 patients who had a neck dissection. Seven children, aged 4.0 to 19.5 years, received postoperative radiotherapy, with doses ranging from 50 to 65 Gy; radiotherapy included the neck area in 5 cases and was associated with concurrent chemotherapy in 2 cases.

At latest follow-up, 15 patients were alive without disease, 1 had died 6 months after surgery from persistent local disease, 1 had died of his original cancer (medulloblastoma), and 1 had been lost to follow-up. For the 15 patients alive at latest follow-up, the median follow-up was 3.5 years (range, 2 to 16 years). The estimated overall survival rates at 3 and 5 years after treatment were 100% and 100%, respectively. The estimated cancer-specific survival rates at 5 and 10 years after treatment were 100% and 100%, respectively. Disease progression occurred in 3 patients, including 2 with local relapses, both with low-grade MEC, and 1 local and regional relapse associated with distant disease in a high-grade MEC. The survival analysis for individual clinical and pathologic features (sex, age, clinical stage, primary tumor site, grade) was not possible because of the small number of events. No sequelaes were observed among the 7 children treated with postoperative radiotherapy, with a median follow-up of 24 months (range, 0.5 to 10 years).

Among 18 MEC cases, 11 patients had a history of a first cancer during childhood, including 4 acute lymphoid leukemias, 2 non-Hodgkin's lymphomas, 1 Hodgkin's disease, 2 brain tumors (medulloblastoma, astrocytoma), 1 rhabdomyosarcoma of a limb, and 1 retinoblastoma (Table 1). The median age at the first cancer occurrence was 5 years (range, 4 months to 18.5 years). The median interval time between first cancer and MEC diagnosis was 5.5 years (range, 1 to 13 years).
Table 1. Description of the original and secondary cancers.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Histology</th>
<th>Treatments</th>
<th>First cancer</th>
<th>Age, y</th>
<th>TNM Stage</th>
<th>Site</th>
<th>Pathologic grade</th>
<th>Treatment</th>
<th>Relapse, mo</th>
<th>Follow-up, y</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>5.1</td>
<td>Astrocytoma</td>
<td>S, XRT (50 Gy), C</td>
<td></td>
<td>9</td>
<td>T2N0</td>
<td>Parotid</td>
<td>I</td>
<td>S</td>
<td>16</td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>5.5</td>
<td>Acute lymphoblastic leukemia</td>
<td>C, BMT, TBI</td>
<td></td>
<td>18.5</td>
<td>T2N0</td>
<td>Parotid</td>
<td>II</td>
<td>S</td>
<td>4.5</td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>6.5</td>
<td>Non-Hodgkin's lymphoma</td>
<td>C</td>
<td></td>
<td>10.5</td>
<td>T1N0</td>
<td>Submandibular</td>
<td>II</td>
<td>S</td>
<td></td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>11.5</td>
<td>Acute lymphoblastic leukemia</td>
<td>C, BMT, TBI</td>
<td></td>
<td>17</td>
<td>T3N0</td>
<td>Parotid</td>
<td>I</td>
<td>S</td>
<td>2</td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>0.3</td>
<td>Bilateral retinoblastoma</td>
<td>S, XRT (52 Gy)</td>
<td></td>
<td>9</td>
<td>T2N0</td>
<td>Parotid</td>
<td>I</td>
<td>S</td>
<td>10.5</td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>11</td>
<td>Medulloblastoma</td>
<td>S, C, XRT (55 Gy)</td>
<td></td>
<td>14</td>
<td>T1N0</td>
<td>Parotid</td>
<td>I</td>
<td>None</td>
<td>0.5</td>
<td></td>
<td>Dead from medulloblastoma</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>18.5</td>
<td>B-cell lymphoma</td>
<td>C</td>
<td></td>
<td>19.5</td>
<td>T2N0</td>
<td>Parotid</td>
<td>I</td>
<td>Unknown</td>
<td>0</td>
<td></td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>2.5</td>
<td>Acute lymphoblastic leukemia</td>
<td>C</td>
<td></td>
<td>5.5</td>
<td>T2N0</td>
<td>Parotid</td>
<td>I</td>
<td>S</td>
<td>9</td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>5</td>
<td>Hodgkin's disease</td>
<td>C, BMT, XRT (20 Gy)</td>
<td></td>
<td>12</td>
<td>T1N0</td>
<td>Parotid</td>
<td>I</td>
<td>S</td>
<td>2.5</td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>4</td>
<td>Acute lymphoblastic leukemia</td>
<td>C, XRT (18 Gy)</td>
<td></td>
<td>19.5</td>
<td>T4N0</td>
<td>Parotid</td>
<td>I</td>
<td>S, XRT</td>
<td></td>
<td></td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>Female</td>
<td>10</td>
<td>Rhabdomyosarcoma of the limb</td>
<td>S, C</td>
<td></td>
<td>16</td>
<td>T1N0</td>
<td>Parotid</td>
<td>I</td>
<td>S</td>
<td>3.5</td>
<td></td>
<td>Alive</td>
</tr>
</tbody>
</table>

Abbreviations: S, surgery; XRT, radiotherapy; C, chemotherapy; BMT, bone marrow transplantation; TBI, total body irradiation.
patients except 1 had initially received chemotherapy with alkylating agents, including cyclophosphamide in 9 patients. External radiotherapy was also performed in 7 cases, with a dose range of 10 to 55 Gy. MEC occurred within or close to the original radiation treatment field in all 7 cases.

Between the 2 groups of patients presenting with MEC as a first or a second cancer, there was no difference in distribution according to age (p = .4), sex (p = .9), tumor grade (p = .06), and tumor location (p = .06). Distribution according to the clinical stage (stage 1–2 vs stage 3–4) did differ (p = .03), with more advanced clinical stage in the group with MEC as first cancer. Differences in overall survival, specific survival, and disease-free survival were not statistically significant between the 2 groups.

**DISCUSSION**

MEC of the salivary glands represents .08% of cancer in the pediatric population, and nearly 45 cases have been reported in the literature. Only 5% of salivary gland MECs arise during childhood and seldom before the age of 10. The clinical and pathologic features are similar in pediatric and adult populations. The most frequent clinical presentation is an isolated, hardened, noninflammatory, painless, and slow-growing tumefaction. In children, as in adults, tumors arise from the parotid gland in 66% of cases and involve the superficial lobe in 75% of cases. The presence of adenopathies depends on grade, size, and location of tumor. They are more frequent in cases of submandibular gland MEC. Distant metastases, mostly in the lung, are rare and indicate a poor prognosis.

FNAB is a well- tried technique for the diagnosis of salivary gland mass. In our series, it was performed in 6 cases, but only 2 procedures allowed correct MEC diagnosis. Pathologic diagnosis and tumor grading were better performed on the surgical specimen. FNAB could lead to misidentification and diagnostic delays, perhaps because most MECs are low or intermediate grade.

Definitive surgery gave very good local control rates in our series and in the literature. A systematic neck lymph node dissection is recommended in patients with advanced-stage disease and high-grade tumors; neck lymph node metastasis is detected in 50% of these cases. In children, postoperative radiotherapy has to be well codified because of the risks of long-term sequelae, but it seems justified in patients with advanced-stage disease and high pathologic grade tumors, which have the worst prognosis in MEC, among both adults and children. Perineural or vascular spread and lymphatic emboli are also pejorative factors, but they appear to be rare in children with MEC. Patients with a facial palsy or paresis have a poor prognosis, although in our series, the only patient with a facial palsy had a favorable outcome. Children with malignant tumors, of whatever histologic type, have a 5-year overall survival rate of 70% and a 3.2% risk of the development of a second cancer during the following 20 years. MEC of the salivary glands represents 6% of these second cancers and is also known to arise as a second malignant tumor in adulthood.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age, y</th>
<th>TNM</th>
<th>Stage</th>
<th>Site</th>
<th>Pathologic grade</th>
<th>Treatment</th>
<th>Follow-up, y</th>
<th>Relapse (mo)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Female</td>
<td>4</td>
<td>T1N0</td>
<td>1</td>
<td>Parotid</td>
<td>I</td>
<td>S, XRT</td>
<td>3</td>
<td>Local (5)</td>
<td>Alive</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>13</td>
<td>T2N1</td>
<td>3</td>
<td>Parotid</td>
<td>I</td>
<td>S, XRT</td>
<td>2</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>12</td>
<td>T2N1</td>
<td>3</td>
<td>Parotid</td>
<td>II</td>
<td>S, XRT</td>
<td>2</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Female</td>
<td>17</td>
<td>T3N1</td>
<td>4</td>
<td>Accessory salivary gland (tonsil area)</td>
<td>III</td>
<td>S, XRT, C</td>
<td>0.5</td>
<td>Local, regional, and distant (3)</td>
<td>Dead from local persistent disease</td>
</tr>
<tr>
<td>16</td>
<td>Female</td>
<td>9</td>
<td>T2N0</td>
<td>1</td>
<td>Parotid</td>
<td>I</td>
<td>S, XRT</td>
<td>10</td>
<td>Local (12)</td>
<td>Alive</td>
</tr>
<tr>
<td>17</td>
<td>Male</td>
<td>11</td>
<td>T1N0</td>
<td>1</td>
<td>Accessory salivary gland (palate)</td>
<td>II</td>
<td>S</td>
<td>5</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Female</td>
<td>15</td>
<td>T1N1</td>
<td>3</td>
<td>Submandibular</td>
<td>III</td>
<td>S, XRT, C</td>
<td>6.5</td>
<td>Alive</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MEC, mucoepidermoid carcinoma; S, surgery; XRT, radiotherapy; C, chemotherapy.
cancers could result from cytotoxic treatment (e.g., radiotherapy, anthracyclines, epipodophyllotoxin, or alkylating agents), combined to a greater or lesser extent with genetic factors. Only 22 cases of salivary gland MEC occurring as a second cancer in the population younger than 20 years have been reported so far (Table 3). In this group of 22 patients, the median age at the first cancer was 5 years (range, 1 month to 14 years), and the median time between the 2 cancers was 7 years (range, 3 to 14 years), which matches our results. We can suspect a role of radiotherapy in the risk of MEC because most of the MECs occurred inside the previously irradiated field, similar to our series. We also noticed that cyclophosphamide was frequently used in the treatment of the first cancer. Most of the first cancers were acute leukemia, especially lymphoid type. In our series, only 4 first cancers were acute leukemias, but that could result from selection bias (Table 1).

In cases of MEC occurring inside the previously irradiated field, the decision whether to administer radiation therapy treatment has to be discussed case by case for high-grade and advanced tumors.

In the subgroup of patients with MEC as second tumor, there were more early-stage tumors ($p = .03$), probably explained by the follow-up of pediatric oncology departments, with the earlier additional examinations. Also small-tumor first cancers could be treated by surgery alone, without treatment by pediatric oncology.

MEC as a second tumor does not affect survival of young patients. However, patients with MEC as a first cancer who presented at a more advanced clinical stage (stage 1–2 vs stage 3–4) ($p = .03$) than those with MEC as second cancer also received postoperative radiotherapy more frequently.

To our knowledge, this is the first work to compare a series of MEC as first and as second cancer. The overall survival and the specific survival did not differ between the 2 groups, although distribution by stage did differ. This may be explained by the good preview of these

**Table 3.** Review of the literature concerning second cancers localized to the salivary glands, 22 cases published in 12 publications.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>No. of patients</th>
<th>Sex</th>
<th>Age, y</th>
<th>First cancer</th>
<th>Second cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Loc</td>
<td>Age, y</td>
</tr>
<tr>
<td>Atahan et al$^{29}$</td>
<td>1</td>
<td>F</td>
<td>6</td>
<td>ALL</td>
<td>13</td>
</tr>
<tr>
<td>Kaste et al$^{2}$</td>
<td>7</td>
<td>—</td>
<td>Mean=5</td>
<td>4/7 ALL</td>
<td>Mean=8</td>
</tr>
<tr>
<td>Prasannan et al$^{30}$</td>
<td>2</td>
<td>—</td>
<td>1.8</td>
<td>ALL</td>
<td>7.8</td>
</tr>
<tr>
<td>Berridge et al$^{31}$</td>
<td>1</td>
<td>F</td>
<td>3</td>
<td>ALL</td>
<td>9.5</td>
</tr>
<tr>
<td>Zappia et al$^{32}$</td>
<td>2</td>
<td>M</td>
<td>4.5</td>
<td>AML</td>
<td>10</td>
</tr>
<tr>
<td>Socié et al$^{33}$</td>
<td>1</td>
<td>F</td>
<td>9</td>
<td>ALL</td>
<td>15</td>
</tr>
<tr>
<td>Loy et al$^{34}$</td>
<td>2</td>
<td>F</td>
<td>15.5</td>
<td>Thyroid</td>
<td>19</td>
</tr>
<tr>
<td>Rodriguez-Cuevas and Ocampa$^{35}$</td>
<td>1</td>
<td>M</td>
<td>3</td>
<td>ALL</td>
<td>6</td>
</tr>
<tr>
<td>Sandoval and Jayabose$^{36}$</td>
<td>1</td>
<td>M</td>
<td>7.5</td>
<td>NHL</td>
<td>15</td>
</tr>
<tr>
<td>Walker et al$^{37}$</td>
<td>2</td>
<td>F</td>
<td>14.7</td>
<td>AML</td>
<td>18.3</td>
</tr>
<tr>
<td>Leung et al$^{38}$</td>
<td>1</td>
<td>F</td>
<td>5.5</td>
<td>AML</td>
<td>9.6</td>
</tr>
<tr>
<td>Myer$^{39}$</td>
<td>1</td>
<td>M</td>
<td>2</td>
<td>ALL</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloblastic leukemia; ALL, acute lymphoblastic leukemia; allo-BMT, allogeneic bone marrow transplantation; auto-BMT, autologous bone marrow transplantation; C, chemotherapy; CNS, central nervous system; F, female; L, lymphadenectomy; M, male; m, mean; NHL, non-Hodgkin's lymphoma; P, parotid; R, radiotherapy; Re, remote; SM, submandibular; Sm, submandibulectomy; TBI, total body irradiation; TP, total parotidectomy; Pe, peripheral to field; PP, partial parotidectomy; W, within field.
cancers and by an adapted treatment for advanced tumors.

CONCLUSION

The clinical presentation and prognosis of MEC appear to be similar in children and in adults. Surgery is the treatment of choice, associated with neck dissections for advanced-stage and for high-grade tumors. Postoperative radiotherapy should also be performed for aggressive tumors, but without ignoring the consequences on craniofacial skeletal growth and the risk of radio-induced second cancers.

MEC in children may frequently occur as a second cancer without significantly influencing the prognosis. A consensus has been reached among the French pediatric units concerning the necessity for long-term follow-up of every patient cured of cancer during childhood with a particular concern about any salivary gland tumefaction.

Acknowledgments. The authors thank the teams of the pediatric oncology departments of the following Children’s Hospitals (Trousseau in Paris, La Timone in Marseille) and of Pediatric Hematology of St. Louis Hospital (Paris).

REFERENCES