Metastatic Adenoid Cystic Carcinoma of Salivary Glands: Case Reports and Review of the Literature

Alexander S.D. Spiers, MD, PhD, Dixie Lee W. Esseltine, MD, John C. Ruckdeschel, MD, Jack N.P. Davies, MD, DSc, and John Horton, MB, ChB

Background: Adenoid cystic carcinoma is an uncommon tumor of the salivary gland. Little has been published on the chemotherapy of this neoplasm.

Methods: The literature on this disease is reviewed, and data from seven unpublished cases are presented.

Results: Four patients received cyclophosphamide. One responded, and another had pain relief. The literature review did not identify any single drug or combination that might be regarded as the treatment of choice.

Conclusions: Systematic, multi-institutional studies are required to determine appropriate systemic treatment for metastatic adenoid cystic carcinoma of salivary gland origin.

Introduction

Adenoid cystic carcinoma, first described as "cylindroma" by Billroth in 1859,[1] is a malignant tumor that is commonly classified with the salivary gland tumors, although it may arise in any site where mucous glands exist. Half of these tumors occur in glandular areas other than the major salivary glands, principally in the hard palate, but they also arise in the tongue and in other areas that are the site of minor salivary glands.[2-9] Unusual locations include the external auditory canal, nasopharynx, lacrimal glands, breast, vulva, esophagus, cervix, and Cowper glands.[10-21] The long natural history of this tumor, its propensity for perineural invasion, and its tendency for local recurrence are well known.[3,22-25] Its distinctive microscopic appearance, its ultrastructure, and its biochemistry have been well described.[26-28]

A primary adenoid cystic carcinoma usually is treated with radical surgery.[3,29,30] While radiation therapy has a 96% response rate, it also has a 94% incidence of subsequent local recurrence and is thus a poor treatment when used alone.[31] Planned combinations of surgery with preoperative or, more commonly, postoperative radiotherapy have shown improvement in both local control and survival.[31-34] While many published series incorporate patients with several varieties of salivary gland tumor, only a few report exclusively on adenoid cystic carcinoma,[31] and information concerning the treatment of advanced adenoid cystic carcinoma is limited.

Most patients with metastatic disease are relatively asymptomatic and may remain so for long periods. Because of the rarity of malignant tumors of the salivary glands, cytotoxic chemotherapy for metastatic disease has not been studied extensively. Due to the heterogeneity of patients with salivary gland tumors, few studies have been done on chemotherapy that was administered specifically for metastatic adenoid cystic carcinoma.

Report of Cases

Case 1. - A 43-year-old woman had two years of persistent jaw pain until a right submandibular mass was detected. Biopsy showed adenoid cystic carcinoma in the base of the tongue. A composite resection was performed following 70 Gy of radiation. The tongue was diffusely involved, including the medial and posterior resection margins, while the lymph nodes, submandibular salivary glands, and mandible were not involved. A bone graft to the area was removed 19 months later, and local recurrence was documented. Concurrently, a pulmonary lesion was seen on chest radiograph. Bilateral pulmonary lesions were present one year later, and the patient received Laetrile without benefit. Twenty months after the original recurrence, neck pain developed, as well as dysphagia and respiratory distress that required tracheostomy and feeding gastrostomy. No lymphadenopathy occurred, but the liver extended 2 cm below the costal margin, and liver biopsy revealed poorly differentiated adenoid cystic carcinoma. Intravenous administration of 1000 mg/m² of cyclophosphamide every three weeks was begun. Her pain disappeared after two courses, but she discontinued therapy because of nausea. Progression of tumor was noted three months later.

Case 2. - A 72-year-old man had a history of a painless mass, which was located in front of the right ear and was resected at 43 years of age. A 2-cm local recurrence was treated by radical neck dissection at age 50, and pathology revealed adenoid cystic carcinoma. Another local recurrence involving the soft tissues near the ascending ramus of the right mandible was documented at 63 years of age, 20 years after the initial surgery. This was treated with 63.75 Gy of radiotherapy in 39 days. Asymptomatic pulmonary masses were first noted two years later. Twenty-eight months after that, 50 to 100 mg of oral cyclophosphamide daily was begun because of progression in the number and size of the pulmonary lesions (Fig 1A). The patient's disease remained stable for 39 months, at which time progression of pulmonary lesions and new rib involvement were noted (Fig 1B). Cyclophosphamide was replaced with 20 mg daily of megestrol. Slow progression of disease continued over the next nine months.

Case 3. - A 48-year-old man complained of swelling of his left cheek of several months' duration. Examination revealed swelling in the left buccogingival fold with no intranasal pathology. Radiographs showed that the left antrum was clouded, with erosion of the anterior wall. A biopsy showed adenoid cystic carcinoma. The tumor extended to the pterygoid fossa and involved the anterior and lateral wall of the antrum but not the posterior wall. Preoperative radiotherapy was administered, followed by left maxillectomy. A small focus of residual adenoid cystic carcinoma was found in the resected specimen. Radiographs detected pulmonary metastases five years later. A bone scan 18 months later showed increased uptake in the left ribs, lumbarosacral spine, and left proximal femur (Fig 2). Local radiotherapy gave good palliation. Masses then developed over the left 11th rib posteriorly and the right eighth rib. The 11th rib was removed, and a biopsy of a pulmonary nodule was done three months later. Both specimens showed adenoid cystic carcinoma. The patient was given 1000 mg/m² of cyclophosphamide intravenously every three weeks,
which resulted in a marked reduction in pain, modest shrinkage of the pulmonary nodules, and complete regression of the rib masses. Eight months after beginning chemotherapy, cyclophosphamide administration was changed from intravenous to oral administration to alleviate nausea. The bone and pulmonary disease remained stable, and no recurrence of the soft tissue masses was seen.

Case 4. A 52-year-old man underwent resection of a left submandibular salivary gland tumor that was found to be an adenoid cystic carcinoma. Local recurrences were resected at 22 and 29 months after the original surgery. Multiple asymptomatic pulmonary nodules were detected at 44 months, and a new 1.5-cm submandibular mass was found at 45 months. Administration of 1000 mg/m² of cyclophosphamide intravenously every three weeks was begun. No recurrence of tumor was seen, and the pulmonary lesions and the soft tissue mass remained stable for six months.

Case 5. A 58-year-old woman noted a mass in her left submandibular area. She developed back pain one month later. A chest radiograph showed pulmonary nodules. Open biopsies of the lung and of a pleural nodule revealed metastatic tumor with an adenoid cystic pattern. The left submandibular salivary gland was resected one month later and was almost completely replaced by adenoid cystic carcinoma. The patient was given 58.90 Gy of postoperative radiotherapy to the submandibular area. The pleural nodules gradually progressed, and a tumor implant developed in the thoracotomy scar. She received treatment with a modified three-day CAF regimen consisting of 400 mg/m² per day of cyclophosphamide, 40 mg/m² per day of doxorubicin, and 200 mg/m² per day of fluorouracil. Doses were increased 40% following the first treatment because hematologic tolerance was good. After three courses of CAF, a computed tomography (CT) scan of the chest showed no change in the pleural nodules or the metastases in the lung parenchyma (Fig 3). Radiation was administered to the tumor implant on her chest with some response, and she was observed without further chemotherapy. Three months later, and 18 months after initial surgery, she developed back pain and blurred vision. A CT scan showed multiple bilateral small metastases in the brain, and ophthalmoscopic examination disclosed numerous metastases in the choroid of the right eye. Two lumbar punctures were negative for tumor cells. She was given dexamethasone and whole brain irradiation. 32 Gy in eight fractions, which resulted in a decrease in the size of the brain metastases as well as the retinal tumor deposits. She developed a perforated pyloric ulcer and required emergency laparotomy with vagotomy and pyloroplasty. At 20 months from diagnosis, she required further radiotherapy for an extradural metastasis in the lower thoracic spine. Over the next three months, she received four courses of cisplatin, initially with no response and then with frank progression of disease, manifested by the development of multiple subcutaneous metastatic nodules. Two doses of mitomycin C were administered without response. She died 26 months after her initial presentation.

Case 6. A 44-year-old man had an 18-month history of pain in the left side of the mandible and a five-month history of deviation of the tongue to the left. Examination disclosed a left submandibular mass, mild left proptosis, and atrophy of the left side of the tongue. A chest radiograph showed multiple bilateral small nodules. A biopsy of the submandibular mass revealed adenoid cystic carcinoma and cytology from bronchial washings was class II. He received three courses of cisplatin, each consisting of 60 mg/m² on two successive days, which resulted in a modest reduction in the size of the pulmonary nodules. Because of local pain, the primary tumor was treated with radiotherapy at a dose of 66 Gy with good response. He was followed without further therapy, and gradual progression of the pulmonary metastases occurred. A cytologically positive right pleural effusion developed 23 months after his initial presentation. Radiotherapy was required five months later for right lower chest pain, and hepatic metastases were detected by ultrasound examination. He received two courses of cisplatin with doxorubicin and cyclophosphamide without objective response. Treatment thereafter was palliative; disease progression occurred, but the patient survived an additional eight months after the onset of palliative care.

Case 7. A 49-year-old man complained of a sore throat. Physical examination showed mild erythema, and an antibiotic was prescribed. A CT scan of the submandibular area showed a subtle abnormality that was appreciated only on retrospective review. A follow-up physical examination nine months later disclosed a mass in the floor of the mouth and three nodules in the base of the tongue, which were confirmed by magnetic resonance imaging. Multiple biopsies were all positive for adenoid cystic carcinoma. A radical resection was performed, and the operative specimen showed invasion of the lingual nerve and one of 27 lymph nodes involved by tumor. Postoperative radiotherapy at 65 Gy was administered. A chest CT scan 17 months later showed two nodules presumed to be metastases. Eight months after that, a repeat chest CT scan showed increases in the size and the number of the pulmonary nodules. At 49 months postsurgery and 32 months after the first demonstration of pulmonary metastases, the patient is asymptomatic, and no further therapy has been administered.

Discussion

The patients in this review were between 43 and 58 years of age at the time of diagnosis. The usual peak incidence of adenoid cystic carcinoma is between 50 and 60 years of age, with tumors seldom occurring before the age of 30 years. The times from initial diagnosis to first local recurrence were 19, 22, and 84 months (Table 1). Three patients did not develop local recurrence, and the primary tumor was not resected in one patient. The times from initial diagnosis to the finding of metastatic disease varied from 0 months (ie, simultaneous finding of primary tumor and metastases) to 264 months (22 years). The lung was the site of first metastasis in all seven patients. Lymph node metastasis was documented only in Case 7. The primary sites were salivary glands in four patients, tongue in two, and maxillary sinus in one. Six patients underwent resection of the primary tumor, and four received radiation therapy either before or after surgery. Pain at the site of the primary tumor occurred in five patients. Asymptomatic pulmonary metastases developed in all seven patients. In Case 3, bone involvement caused severe pain, bone destruction on radiograph (Fig 1A), and a positive bone scan. Although rib metastases adjacent to the pulmonary metastases developed in Case 2 (Fig 1B), the patient remained asymptomatic.

Of four patients who were treated with single-agent cyclophosphamide (Table 2), two experienced pain relief. In one of these two, pulmonary nodules regressed, but the regression was insufficient to constitute a partial remission. While stationary disease of six months and 39 months was seen in the remaining two patients, its significance is questionable in a tumor that is well known for its frequently indolent course, and chemotherapy may have played no part in the apparent lack of disease progression. The fifth patient received three separate chemotherapy regimens with no response. The sixth patient experienced a minor and clinically insignificant regression of pulmonary nodules in response to single-agent cisplatin but subsequently failed to respond to a multiple-agent chemotherapy regimen. The seventh patient remains asymptomatic with small, indolent pulmonary nodules, and chemotherapy has not been administered.

Adenoid cystic carcinomas in the head and neck have been treated most frequently with surgical resection, but the combination of surgery with preoperative or postoperative irradiation improves both local control of disease and disease-free survival. The rarity of lymph node metastasis suggests that radical node dissection is not warranted in the absence of clinical or radiographic evidence of lymph node involvement.
The paucity of literature relating to chemotherapy for adenoid cystic carcinoma stems in part from the relative rarity of these tumors. Also, data relating to treatment for salivary gland tumors of other histologic types, as well as to chemotherapy for squamous cell lesions of the head and neck, tend to be included. Koop et al[36] reported some improvement with oral cyclophosphamide in a patient with pulmonary metastases. A review was conducted in 1977 at the M.D. Anderson Hospital in Houston, Texas, of its 25-year experience of patients with malignant neoplasms of the major salivary glands.[37] Of 671 patients, 43 (6%) received single-agent chemotherapy with one of 21 phase I and II agents. Four partial responses (10%) were observed in 39 evaluable trials. Three of six patients treated with an anthracycline and one of two treated with hexamethylmelamine (altretamine) responded. Of 23 evaluable trials with multiple-agent chemotherapy, responses occurred in one of four patients who received cyclophosphamide and lomustine and in one of three who were treated with fluorouracil, mitotane, lomustine, and BCG. Of 17 patients who received 34 adequate trials of chemotherapy at the Princess Margaret Hospital in Toronto, Canada, five responses were noted overall; four of these occurred in 12 patients who received weekly doses of fluorouracil.[38]

Schramm and colleagues[39] treated 10 patients with persistent, recurrent, or metastatic adenoid cystic carcinoma with single-agent cisplatin at doses of 80 to 100 mg/m² every four to six weeks until discontinued due to renal toxicity, patient refusal, disease progression, or complete response. Pain relief occurred in seven of 10 patients. Partial or complete tumor regression occurred in four of five patients with local disease and in three of six patients with metastatic disease, including a patient with a cerebral metastasis. Complete responses lasting seven to 18 months were noted in four patients. In a report by Alberts et al[40] of five patients treated with a combination of doxorubicin, cisplatin, and cyclophosphamide, complete responses lasting five months were seen in two patients, and partial responses of one, six, and seven months were seen in three patients. Administering the same combination of drugs but at different doses and schedules, another group[41] noted an overall response rate of 50% in 16 patients. Eisenberger[42] also reported favorable results in four patients - three complete remissions and one partial remission - with doxorubicin, cisplatin, and cyclophosphamide. Cisplatin also had been administered by the intra-arterial route to patients with adenoid cystic carcinoma, and all four patients showed some response.[43] In 1982, Suen and Johns[44] gathered from the literature 39 evaluable cases of various subtypes of carcinoma of the salivary glands. A questionnaire sent to 25 oncologists provided information on another 46 patients, in which the overall response rate to cytotoxic chemotherapy was 42%.

More recently, the combination of cisplatin with fluorouracil has undergone extensive study in patients with head and neck cancer. The majority of the patients studied had squamous cell carcinomas, but patients with adenocystic carcinoma who had objective responses were included occasionally.[45] Another study of the combination of doxorubicin, cisplatin, and cyclophosphamide confirmed its activity in adenocystic carcinoma and suggested that this chemotherapy regimen might be of value as an induction treatment before surgery and/or radiation therapy.[46] Dimery et al[47] treated 17 patients with salivary gland carcinomas with a combination of fluorouracil, doxorubicin, cyclophosphamide, and cisplatin. Among the seven patients with adenoid cystic carcinoma were three partial responses, two minor responses, and two with stationary disease. A report from Turin University[48] of 27 patients, including 10 with adenocystic carcinomas, found some superiority for multiple-agent regimens with an overall response rate of 45%, but Licitra et al[49] of the Istituto Nazionale Tumori in Milan did not find multiple-drug therapy to be superior and reported an overall response rate of 27%. Vermorken et al[50] conducted a study of epirubicin used to treat 20 patients with adenoid cystic carcinoma. Unlike many studies, theirs was confined to a single histologic subtype of salivary gland tumor. Objective regression occurred in two (10%) patients, but symptomatic improvement occurred more often. All patients had documented progressive disease before treatment, and 10 (50%) showed disease stabilization with a median time to progression of 16 weeks (range 2-250 weeks).

Conclusions

Several single agents, including cyclophosphamide, fluorouracil, doxorubicin, and cisplatin, have significant activity in adenoid cystic carcinoma of the salivary glands. Reports of small series have suggested that combinations of two, three, or all four of these drugs produce superior activity, but results are conflicting, and no therapeutic regimen has emerged as the undisputed treatment of choice. The long natural history and indolent progression of adenoid cystic carcinoma make "stationary disease" a poor criterion of response to treatment. While further clinical research into the chemotherapy of metastatic adenocystic carcinoma is warranted, there also is an equal need to recognize that many patients with asymptomatic and indolent disease fare better and enjoy a better quality of life without the chemotherapist's intervention.

References