Clinical cases

Small-cell carcinoma of the esophagus: Report of three cases and review of the literature with emphasis on therapy

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Summary

Primary small-cell carcinoma (SCC) of the esophagus is rare, with about 200 cases reported up till now in the literature. Like pulmonary SCC, it is an aggressive tumor associated with a poor prognosis. Between 1994 and 1997, three patients with SCC of the esophagus were treated at Besançon University Hospital and this represented 1.85% of all esophageal malignancies diagnosed during this period. One patient had a limited tumor and underwent initial surgical resection, then chemotherapy with cisplatin and etoposide, and radiotherapy for recurrences. The other patients had extensive disease at diagnosis and were treated by the same chemotherapy.

This retrospective study reports our experience of patients with this particular tumor and outlines the management strategy based on the available literature.

Key words chemotherapy, esophagus, small-cell carcinoma

Introduction

Small-cell carcinoma (SCC) is a distinct pathologic entity first described in the lung. It accounts approximately for 20% of all bronchogenic carcinomas. The occurrence of primary extrapulmonary tumors has been described in other organs, namely nasal cavities and paranasal sinuses, larynx, hypopharynx, salivary glands, thymus, esophagus, stomach, pancreas, small and large intestines, cervix and endometrium, prostate and bladder, breast and skin [1-5]. About 5% of the SCC have an extrapulmonary origin. Primary SCC of the esophagus was first described in 1952 by McKeown who reported two cases without pulmonary tumor at postmortem examination [6]. About 200 cases have since been reported in the literature. Esophageal SCC has been reported with a variable incidence of 0.5%-2.4% in the different series [7, 8]. Japanese studies have even shown an incidence of up to 15% of all esophageal tumors [9]. Like pulmonary small-cell carcinoma, SCC of the esophagus is an aggressive tumor associated with a poor prognosis and a mean survival of 6-7 months [10, 11]. Different forms of treatment have been used, including chemotherapy, radiation therapy or any combination of these with few reports of longer survival. This retrospective study reports the case histories of three patients with small-cell carcinoma of the esophagus who were recently referred to our institution and for whom polychemotherapy was a major part of treatment.

Case reports

Case 1

A 69-year-old man came to our institution in September 1994 with dysphagia. He was a social drinker of alcohol and had a history of smoking (eight pack-years). Performance status was 0 and physical examination was normal. A chest X-ray showed an enlarged mediastinum. Oesophagoscopy revealed a narrowing tumor 6 cm in length, in the middle third of the esophagus and histologic analysis of the biopsies concluded a small-cell carcinoma (SCC) in view of round to spindle-shaped cells with scanty cytoplasm, granular nuclei, inconspicuous nucleoli (Figure 1) and immunohistochemical evidence of neuroendocrine differentiation: many cells were reactive with antieneolase neurospecific antibody and antichromogranine A. A computed tomography (CT) scan showed an esophagus tumor with enlarged mediastinal lymph nodes without any abnormality in the chest or abdominal space. Bronchoscopy and cytology were normal, as well as bone scintigraphy and brain CT scan. The patient was therefore staged as having T2 or T3 N1 M0 SCC of the esophagus.

The primary treatment was esophagectomy with lymphadenectomy, which confirmed the histology. The resection margins were clear and metastasis was seen in a single lymph node. The staging was then pT3 pN1 M0. No adjuvant therapy was proposed.

In February 1995, three months after the surgery, the patient was admitted because of asthenia and high weight loss with anorexia. Physical examination recorded...
bilateral sub-clavicular and cervical lymphadenopathies. Standard biological examinations were normal. Screening for tumor markers revealed a high serum level of neuron specific enolase (NSE). Oesophagoscopy did not show any local recurrence. A thoracic CT scan showed enlarged mediastinal lymph nodes and lung metastasis. Brain CT scan was normal.

The patient received six courses of cisplatin 100 mg/m$^2$ from day 1 and etoposide (VP16) 100 mg/m$^2$ from day 1 to 3, every three weeks. Tolerance to treatment was good.

After six courses, a complete response was achieved in view of the thoracic and abdominal CT scan and NSE was normalized.

In February 1996, six months after the end of chemotherapy, a new CT scan showed a mediastinal recurrence. The patient was then treated with radiotherapy: 45 Gy over three weeks to the mediastinum (1.5 Gy x 2/day). Three months after the end of radiotherapy, he complained of general fatigue with loss of 5 kg. Another CT scan showed abdominal lymphadenopathies and a brain CT scan revealed multiple metastasis. The patient subsequently died in July 1996, i.e., 22 months after the diagnosis.

**Case 2**

A 75-year-old woman was admitted in March 1996 with dysphagia, epigastric pain and general fatigue. She had a history of arterial hypertension with renal insufficiency and smoking (five pack-years) until 1986. Performance status was 2 and physical examination was normal. The chest radiograph showed widening of the superior mediastinum attributable to enlarged lymph nodes. Endoscopy showed a tumor of the middle third of the esophagus with an old ulceration of the antrum. The biopsies were characterized by diffuse growth of small cells with scanty cytoplasm, irregular and hyperchromatic nuclei, in fibrous conjunctive tissue. Immunohistological study showed reactivity with antienolase neurospecific antibody, but not with antichromogranine A antibody. A thoracic CT scan showed an anterior extensive mediastinal mass 9 cm in length under the carina surrounding the descendant aorta with mediastinal lymph node (Figure 2a). Bronchoscopy with cytology was normal. An abdominal CT scan revealed multiple para-aortic and coeliac lymphadenopathies and abnormal hypodensity in the spleen. Hot spots in the left coxofemoral articulation and in left shoulder were also noted at bone scintigraphy.

A diagnosis of metastatic SCC of the esophagus was made and multi-drug chemotherapy was decided with reduced doses because of age and renal insufficiency. She received cisplatin 60 mg/m$^2$ from day 1 and etoposide 80 mg/m$^2$ from day 1 to 3, every three weeks. After three courses, esophagoscopy showed a residual rigidity over only 3 cm. A CT scan showed a partial response, with 75% tumor and lymphadenopathy size reduction. Chemotherapy was continued with six courses, and sub-
Figure 3  Endoscopic ultrasonography showing the involvement of the muscularis and large right and left paratracheal lymph nodes

subsequently endoscopy and a CT scan demonstrated a complete response (Figure 2b).

In March 1997, she complained of general fatigue with extended pain, related to diffuse bone metastasis. Another oesophagoscopy showed a local recurrence with stenosis of the middle third of the esophagus. Palliative treatment was decided and the patient died in April 97, i.e., 14 months after the diagnosis.

Case 3

A 48-year-old man came to the hospital in April 97 because of dysphagia for three months with general fatigue, loss of 5 kg and retrosternal pain. He had history of subtotal gastrectomy because of a perforating ulcer. He was a former alcohol drinker and had smoked 25 pack-years until 1995. He was a tradesman and suffered from occupational intoxication by dioxin. A physical examination was normal. Chest X-ray showed an enlarged mediastinum and esophagoscopy revealed a lobulated mass 24 to 30 cm from the incisor teeth, with ulceration and infiltration. Biopsies agreed with the diagnosis of SCC in view of infiltration of the epithelial and subepithelial connective tissue by a small cell malignant tumor with scanty cytoplasm, increased nuclei and inconspicuous nucleoli. An immunohistochemical study showed both epithelial and neuroendocrine differentiation with epithelial membrane antigen, antienolase neurospecific antibody and chromogranine A. Serum tumor markers revealed a high serum level of neuron specific enolase (NSE). An endoscopic ultrasonography was performed showing tumor involvement of the muscularis propria with very large right and left paratracheal lymph nodes (Figure 3). An abdominal CT scan echography showed liver metastases and bilateral surrenal metastases. Multiple hot spots were discovered with bone scintigraphy. A cervico-thoracic CT scan did not show any pulmonary lesions. Bronchoscopy and cytology were negative.

The patient was treated with chemotherapy: cisplatin 100 mg/m² from day 1 and etoposide 100 mg/m² from day 1 to 3, every three weeks. After three courses, clinical improvement was obtained and NSE was normalized. After six courses, a thoracic CT scan showed a complete tumor and lymph nodes response. Another endoscopic ultrasonography however visualized a residual tumor 2 cm in length up to the muscularis tissue, and residual lymphadenopathies. Further biopsies showed both epidermoid and SCC. Abdominal echography and bone scintigraphy showed persistent lesions respectively in liver and bones. The patient remained stable and put on 12 kg, and it was decided to stop chemotherapy.

In January 1998, four months after the end of chemotherapy, the patient was admitted because of confusion. A brain CT scan revealed multiple metastases. An association of corticotherapy and brain radiotherapy did not improve the symptomatology and the patient died at the end of January, i.e., 10 months after the diagnosis.

Discussion

Primary SCC involving the esophagus is a relatively recently described entity, and appears to be the most frequently reported digestive tract site of extrapulmonary SCC. The majority of cases have been reported in men, with a male to female ratio of 2:1. The tumor commonly occurs in the sixth to eighth decade. The main symptoms are rapidly progressive dysphagia and weight loss, as for the usual types of esophageal cancer. Involvement occurs at the middle and the lower thirds of the esophagus [11-13].

The exact histogenesis of SCC of the esophagus remains unclear and the origin of the small cells is currently being debated: they were initially thought to arise from argyrophilic Kulchitsky cells, which are found in both bronchial and esophageal mucosa. These cells have the ability to synthesize and store amines and to decarboxylate some amino-acids, giving rise to the term APUD cells. It is now accepted that SCC is of endodermal origin derived from a pluripotential basal epithelial cell, explaining the coexistence of SC, squamous, and glandular elements in the same lesions, a histological pattern which is observed in about 35% of primary SCC of the esophagus. The histology is morphologically identical to the more common bronchial lesions, consisting of round to spindle shaped cells with scanty cytoplasm, granular nuclei, inconspicuous nucleoli, and ultrastructural and immunohistochemical evidence of neuroendocrine differentiation. The cells may be argyrophil positive with neurosecretory granules seen by electron microscopy [14].

These histologic features in addition to the clinical characteristics were observed in our patients.

Because of the similarities with SCC of the lung, it is important to rule out a direct invasion of the esophagus from adjacent mediastinal structures of the lungs. In addition to a thoracic CT scan, a bronchoscopy is mandatory. To our knowledge, endoscopic ultrasono-
raphy has never been used in SCC of the esophagus. This would suggest assessing the deep involvement of the tumor and the extension to the regional lymph nodes in order to improve the TNM staging. In small-cell lung cancer, this classification is considered useful as it is for non small-cell lung cancer, because it is more descriptive and reproducible than the traditional limited-extensive disease system. In our opinion, TNM staging needs to be used in the same way for SCC of the esophagus.

The treatment of SCC of the esophagus remains unclear. Surgical resection, radiation therapy and multiagent chemotherapy, have been used either alone, or in combination. However the prognosis remains poor with a mean survival of 6–7 months [10, 11] with 37% and 10% of patients being alive 6 months and 12 months after treatment respectively [15].

Chemotherapy alone in SCC of the esophagus was first used in 1980 [16]. The patient was treated with combination chemotherapy using cisplatin, etoposide, alternating with cyclophosphamide, doxorubicine and vincristine, with a survival time of nine months. Other reports also suggest that this tumor is as responsive to chemotherapy as the SCC of the lung and there is an emerging consensus in the literature that systemic chemotherapy should be used as part of the treatment program [17–19]. Reports of long survival are rare: one patient with three years survival after treatment by chemotherapy, autologous bone marrow transplantation and radiation therapy [20], one patient with six years survival after surgery followed by chemotherapy and after recurrence by radiotherapy [14], one patient with more than six years survival after neoadjuvant polychemotherapy, radiotherapy and adjuvant chemotherapy [21], and one patient with more than eight years survival after surgery plus adjuvant chemotherapy [22]. Our patients were given cisplatin and etoposide, a common treatment used in SCC of the lung. This treatment was well tolerated and survival duration was comparable to that reported in the literature.

Many different modalities have been used to manage this tumor of the esophagus, and the choice of treatment remains controversial. Whether or not combined modality treatment using concurrent chemo-radiotherapy and additional chemotherapy as widely used in lung SCC is unknown.

Because widespread metastases are frequent at autopsy [17], it can be suggested that a limited stage treatment with chemotherapy be given first. This would determine the tumor sensitivity to the antineoplastic agents and then radiotherapy or surgery can be discussed in the event of an objective response. Very few data about the rationale for surgery are available in such cases, but some institutions consider that surgery with curative intent should be considered as part of multi-modality treatment in selected patients with limited stage disease and perioperative chemotherapy, because the longest survivals seem to be reported in patients treated with esophagectomy combined with chemotherapy and radiotherapy [22, 23].

These concepts of chemotherapy associated or followed by local treatment (radiotherapy and sometimes surgery) could be used as standard treatment, as supported by other recent reports [24] which conclude that the optimal prognostic factor is the application, when possible, of combined treatments.

References

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