Leptomeningeal carcinomatosis associated with oesophageal adenocarcinoma : two case reports and review of the literature

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Abstract

Leptomeningeal carcinomatosis (LC) is a rare complication of solid tumours. We report two cases of leptomeningeal carcinomatosis in patients with oesophageal adenocarcinoma. Diagnosis of LC can be overlooked without a high index of suspicion. Multifocality of symptoms and signs is the hallmark of LC. The combination of cerebrospinal fluid cytology and magnetic resonance imaging has a high diagnostic accuracy. The prognosis remains poor and therefore all therapies are still palliative. (Acta gastroenterol. belg., **2006**, 69, **377-380**).

Key words : meningeal neoplasms, oesophageal neoplasms, adenocarcinoma.

Case 1

A 60-year-old man with an oesophageal mass was referred to our academic hospital for further staging and therapy. He presented with progressive weight loss (20 kilograms in 6 months), intermittent solid food dysphagia, pyrosis and increased salivation. He was a cigarette smoker of half a pack per day, there was no alcohol abuse.

His medical history mentioned coronary bypass surgery in 1996, appendectomy and drainage of a cervical abscess a few weeks before presentation. Family history for cancer was negative.

On examination, his weight was 61 kg and height was 174 cm. The physical examination revealed severe muscle wasting and anaemia. In addition, he was confused with fluctuating levels of consciousness. Clinical neurological examination showed cerebellar ataxia with saccadic eye movements and horizontal jerk nystagmus.

Routine blood and urine analysis demonstrated microcytic anaemia with haemoglobin of 7,5 g/dL (14 to 18 g/dL) and C-reactive protein 11,5 mg/L (< 5 mg/L). Gastroscopy confirmed the presence of a circular (non obstructing), ulcerated mass at 39 to 44 cm from the incisors, with extensions up to 31 cm. The gastro-oesophageal junction was involved. Biopsy of the tumour revealed a moderately differentiated adenocarcinoma.

A computed tomography (CT) demonstrated the tumoural mass at the gastro-oesophageal junction with multiple enlarged locoregional and retroperitoneal lymph nodes. A cranial CT showed an area of hypodensity in the caudate nucleus, whereas a magnetic resonance imaging (MRI) of the brain revealed enhancement of the leptomeninges in the insular cistern bilaterally (Fig. 1).

A lumbar puncture revealed a WBC count of 94 cells/µL (0 to 5 cells/µL), glucose 39 mg/dL (comparison with serum glucose) and protein 300 mg/dL (150 to 450 mg/dL), with microscopic features of malignant cells (very large cells, pleiomorf, granular nuclear chromatine with some prominent nucleoli – some multinuclear and frequently small vacuols).

These findings were consistent with a stage TxN1M1b. Neither chemotherapy nor radiotherapy was initiated given the poor performance status of the patient. He deteriorated rapidly and died 42 days after diagnosis of leptomeningeal carcinomatosis.

Case 2

A 46-year-old man was admitted to our hospital with headache and vomiting since more than one week. Four months earlier he presented with an adenocarcinoma of the distal oesophagus – originating from a Barrett's oesophagus – with mediastinal, hilar and retroperitoneal lymphadenopathy as well as bone metastasis, consisting with a stage TxN1M1b. He received in total five cycles of Epirubicin, Cisplatin and 5-Fluorouracil (ECF) chemotherapy with a radiological good response after the third cycle.

Physical examination as well as mental presentation was normal. Routine blood analysis demonstrated macrocytic anaemia with haemoglobin of 10 g/dL (14 to 18 mg/dL).

A cranial CT showed no abnormality, whereas MRI showed diffuse linear enhancement at the surface of the spinal cord (Fig. 2). A lumbar puncture revealed a WBC count of 15.2 cells/µL (0 to 5 cells/µL), glucose 23 mg/dL (comparison with serum glucose) and protein

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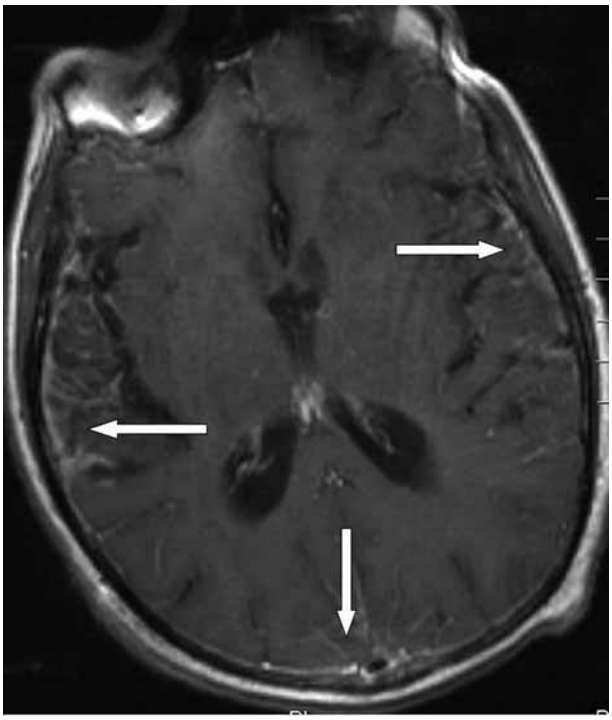

Fig. 1. — Transverse gadolinium-enhanced T1-weighted image shows diffuse thickening and enhancement of the dura of the convexity and of the leptomeninges in the insular cistern bilaterally.

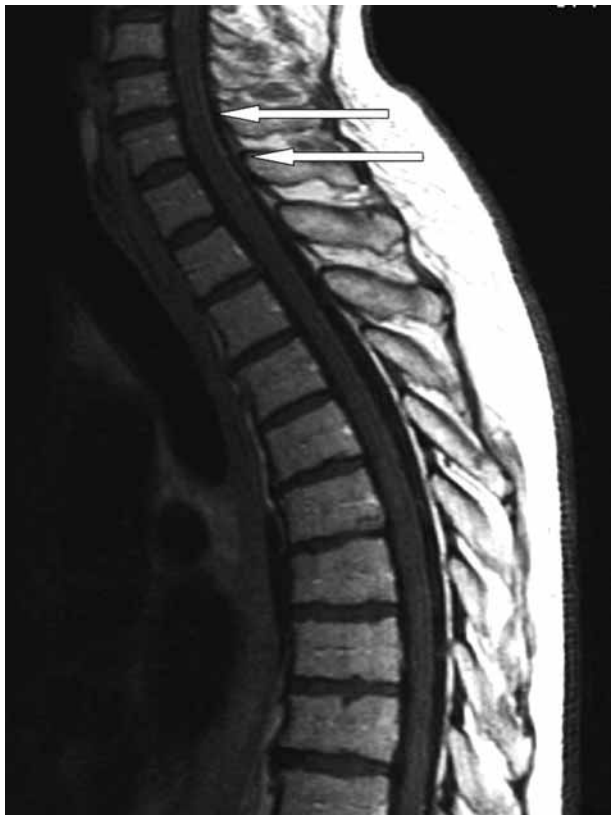

Fig. 2. — Midsagittal gadolinium-enhanced T1-weighted image shows diffuse linear enhancement at the surface of the spinal cord.

1075 mg/dL (150 to 450 mg/dL), with microscopic evidence of malignant cells.

Palliative care with corticosteroids was started. The patient died shortly thereafter, only 17 days after the clinical onset of CNS presentation.

Discussion

In these two patients the diagnosis of advanced adenocarcinoma of the distal oesophagus with leptomeningeal carcinomatosis (LC) was made. LC refers to diffuse seeding of the leptomeninges by malignant cells (originating from a solid tumour or haematologic), gaining entry into the cerebrospinal fluid (CSF). The most common solid tumours associated with leptomeningeal dissemination are breast (12 to 34 percent), lung (10 to 26 percent, particularly small cell lung cancer), melanoma (17 to 25 percent) and carcinomas of unknown primary site (1 to 7 percent) (1-4). The median age at diagnosis is 48,5 years.

LC caused by metastatic oesophageal adenocarcinoma has been rarely reported. A review of the literature found only 4 cases of LC secondary to oesophageal adenocarcinoma (with or without involvement of the gastro-oesophageal junction) (5-8). We did not include adenocarcinoma confined to the stomach (more common cause of LC) in our search. The clinical characteristics and comparison of these patients to our case are summarized in Table 1.

There is a variety of mechanism by which tumour cells invades the leptomeninges. Distant solid tumours can extend along perivascular and perineural lymphatics through vertebral and cranial foraminae. Other routes include haematogenous spread to the vessels of the choroids plexus or meninges (in case of leukaemia) and direct extension from an adjacent parenchymal lesion.

After invading the leptomeninges, tumour cells spread along the route of CSF circulation, seeding the subarachnoid space. Tumour foci may occur throughout the brain or spine surface, as well as within the ventricular system. Most cells are deposited in regions of relative CSF stasis such as the base of the brain (basilar cisterns or posterior fossa) and the base of the spine (cauda equina), which was also the case in our patients. Tumour can also extend along the spinal or cranial nerves or invade the cortex through the Virchow-Robin spaces (9-10).

Clinical manifestations vary and can be divided into three groups : those with invasion of the parenchyma (cortex), those with infiltration of cranial or spinal nerves and those with obstruction of CSF circulation. Common cortical findings include headache, confusion, encephalopathy, gait difficulty and seizures. The most commonly affected cranial nerves are the oculomotor

Table 1. — **Review published cases of leptomeningeal carcinomatosis (LC) from distal oesophageal adenocarcinoma**

	present patient 1	present patient 2	case 1	case 2	case 3	case 4
Age at primary diagnosis	60	46	50	51	49	61
Sex	Male	Male	Male	Female	Male	Male
Location in oesophagus	Lower third plus GE junction	Lower third	Lower third plus GE junction	not clear	Lower third	Lower twothirds
Presenting symptoms	weight loss, dysphagia	weight loss, dysphagia	weight loss, dysphagia	weight loss, gastric pain, dyspepsia	dysphagia, pyrosis	unclear
CNS presentation	decreased LOC, confusion	headache, vomiting	decreased LOC, headache	decreased LOC, confusion, vomiting	decreased LOC, headache, intermittent paralysis, visual loss in both eyes	decreased LOC, confusion
CT findings	area of hypodensity in the caudate nucleus	normal	nodular enhancement of the meninges	enhancement in the caudate nucleus	normal	normal
MRI findings	enhancement of the meninges	enhancement of the meninges	ND	ND	ND	enhancement of the cerebellar meninges
CSF cytology	+	+	+	+	ND	+
Treatment for LC	palliation and corticosteroids	palliation and corticosteroids	palliation and corticosteroids	palliation	palliation	palliation
Outcome	died within 42 days of diagnosis LC	died within 23 days of CNS presentation	died within 20 days of diagnosis LC	died within 5 days of diagnosis LC	died within few months of CNS presentation	died within 17 days of diagnosis LC
Autopsy	ND	ND	ND	confirmed LC	confirmed LC	ND

CNS central nervous system, CT computed tomography, MRI magnetic resonance imaging, CSF cerebrospinal fluid, GE gastro-oesophageal junction, LOC level of consciousness, ND not done.

(III), trigeminal (V), facial (VII) and vestibulocochlear (VIII) nerves. Spinal cord and/or root involvement is characterized by lower motor neuron weakness, radiculopathy, reflex changes, and bowel or bladder dysfunction. Obstruction of the CSF flow produces symptoms related to increased intracranial pressure, such as headache, nausea/vomiting and encephalopathy (11).

The hallmark of LC is the multifocality of symptoms and signs along the neuraxis. Although patients initially may complain of a single symptom, careful neurological examination reveals numerous distinct (subclinical) abnormalities. As LC progresses, established findings worsen while new symptoms and signs appear.

Diagnosis of LC can be overlooked without a high index of suspicion. The diagnostic gold standard is the identification of malignant cells in the CSF, obtained by lumbar puncture. The specificity of cytologic examination is excellent, however the sensitivity is suboptimal. Several lumbar punctures (removing 20 to 40 mL each) may be required to demonstrate malignant cells. Cytology is positive in approximately 55% of the patients with LC upon the first spinal tap and in 90% after the third tap (12). Other CSF characteristics for LC include high protein, low glucose and lymphocytic pleocytosis. The use of biochemical markers (such as carcinoembryogenic antigen from adenocarcinomas) can be useful as adjunctive diagnostic tests and to assess response to treatment when followed serially (4).

MRI is probably more sensitive than a single CSF cytology, but a wide range of sensitivity is reported. No large recent study has looked at MRI sensitivity, although it is in the 70-90% range in detecting intracranial LC (13). Gadolinium-enhanced MRI (particulary T1-weighted images) may reveal focal areas of (linear) contrast enhancement or thickening or nodular deposits in the subarachnoid space, with or without hydrocephalus. Contrast enhancement is not absolutely specific for LC and may be seen with infectious or inflammatory processes, but in a specific clinical setting it may be highly suggestive of LC. If MRI is contraindicated, CT myelography is preferred since contrast-enhanced CT has a low sensitivity of only 44% (14-15).

Both MRI and CSF examination should be used to increase the diagnostic accuracy, with first an MRI because iatrogenic enhancement can result from lumbar puncture. Only in unusual circumstances, leptomeningeal biopsy is necessary to make the diagnosis. In our patients diagnosis was made by the combination of MRI and lumbar puncture.

Radionuclide flow study should be performed before intrathecal chemotherapy is administered, since CSF flow abnormalities prevent homogenous distribution (3).

Without treatment the prognosis of LC is poor. The median survival varies by solid tumour type but is generally not more than 4 to 6 weeks (1,16). Even patients who respond to treatment usually succumb to their disease within 6 to 8 months.

Because of the multifocal involvement, treatment must be directed towards the entire neuroaxis to be effective. To overcome the blood brain-barrier, chemotherapy must be given intrathecally or intraventriculary (via Ommaya reservoir). The three standard chemotherapeutic agents used are methotrexate, cytarabine and thiotepa. Nevertheless there utility in most solid tumours (except for breast cancer) is unclear. Therefore first line therapy may include corticosteroids and radiotherapy of the effected site in an attempt to palliate symptoms, reserving more aggressive interventions for a selected population with a high Karnofsky performance status, minimal neurologic deficits and controlled or slowly progressive systemic malignancy (3-4).

Corticosteroids may improve headache and radicular pain more effectively than analgesics. Radiation therapy provides more rapid relief of symptoms than chemotherapy does. In our patients neither chemotherapy nor radiotherapy was given.

Conclusion

Although LC is a rare complication of oesophageal adenocarcinoma, a high index of suspicion should be maintained when such a patient present with an encephalopathy, cranial nerve palsies or spinal cord/root dysfunction.

CSF cytology is the most valuable test, though several lumbar punctures may be required to demonstrate malignant cells. Therefore a Gadolinium-enhanced MRI of the brain and/or spine should first be performed. Despite greater diagnostic accuracy and earlier diagnosis, all therapies are palliative. Corticosteroids and radiotherapy are the first line of palliation, reserving intrathecal or intraventricular chemotherapy for a selected population.

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