BRAIN METASTASIS AS THE FIRST SYMPTOM OF GASTRIC CANCER – CASE REPORT AND LITERATURE REVIEW

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The study presented a patient with asymptomatic gastric cancer, in whom the first symptom was metastasis to the brain. The patient was initially diagnosed by a neurologist and subject to surgical intervention in the area of residence, where he underwent craniotomy with the excision of the metastatic lesions located in the occipital lobe. The histopathological examination revealed the presence of adenocarcinoma metastases. Following complex diagnostics the patient was diagnosed with cardial carcinoma, being subject to cerebral radiotherapy and chemotherapy. The patient was then referred to surgery at the Wielkopolska Cancer Center in Poznań. After final exclusion of disease dissemination (by means of PET-CT) the patient underwent total gastrectomy with D2 lymphadenectomy, and gastrointestinal tract reconstruction by means of the Roux-en-Y method. The histopathological examination result was as follows: tubular-papillary G2 adenocarcinoma (intestinal type), pT2 pN0 (23 evaluated lymph nodes without cancer metastasis), vascular neoplastic emboli, and positive HER2 protein expression. After surgery the patient was subject to adjuvant chemotherapy. Control brain CT examinations revealed the presence of 4 recurrent metastatic lesions-the patient was disqualified from stereotactic radiation therapy and was subject to palliative chemotherapy. The discussion presented the problem of treating patients with stage IV gastric cancer, including current management guidelines, as well as literature review concerning the treatment of patients with diagnosed gastric cancer and brain metastases.

Key words: gastric cancer, gastric cancer symptoms, gastric cancer metastases, brain metastases

Gastric cancer is one of the most common tumors in the world (1). According to the Globocan registry, in 2008, 998 000 new cases of gastric cancer were recorded, which makes it the fourth most common tumor in the world, after lung, breast and colon cancer (2). In Poland, in 2009, gastric cancer was diagnosed in 5164 patients (3409 male and 1755 female) (3). In terms of the incidence of malignant carcinomas, gastric cancer was the fifth most common tumor, considering male patients, and the ninth in case of female subjects (1). Mortality amounted to 3460 male patients, and 1871 female cases (3).

The most common symptoms reported by the patients were as follows: abdominal pain, dysphagia, nausea, weight loss, and cachexia (4). Lymph nodes metastases are most common- they concern 48% of patients. Vascular metastasis is most common to the liver (37%), lungs (16%) and bones (16%) (5, 6). Gastric cancer metastases to the central nervous sys-
tem are rare, their incidence ranging between 1 and 6% (5, 7, 8).

According to literature data cerebral metastases constitute 20-40% of all intracranial tumors, most often being derived from melanoma, lung and breast cancer (8, 9). Brain metastases from gastrointestinal tumors constitute 4%, of which gastric cancer <1% (7, 8). Approximately, 50% of gastrointestinal tract metastases refer to single lesions (10).

The incidence of gastric cancer brain metastases is continuously increasing. The above-mentioned is associated with significant improvement in diagnostic techniques and oncological treatment, leading towards increased survival considering patients with gastric cancer (improved surgical standards, increased ratio of palliative resections, more effective systemic therapy). Most publications concerning brain metastases include case reports. In literature data there are few reports describing neurological disorders associated with brain metastasis, being the first symptom of gastric cancer in case of an asymptomatic gastrointestinal tract patient (11, 12).

The study presented a case of a patient where the first symptom of gastric cancer was associated with brain metastasis.

CASE REPORT

A 51-year old male patient was admitted to the I Department of General and Oncological Surgery, Wielkopolska Cancer Center (WCC) on September 22, 2011 with diagnosis of gastric cancer.

In march, 2011 the patient visited his primary care physician, due to sudden deterioration of binocular vision. No other symptoms were present. The patient was referred to a neurologist and computer tomography was performed, which revealed the presence of two lesions, 18 and 28 mm in diameter, located in the left occipital lobe and suspected of a metastatic process.

Due to neurological symptoms and the CT examination result the patient was admitted to the Department of Neurosurgery, Provincial Hospital, being subject to surgery on April 4, 2012 (craniotomy and excision of the occipital lobe lesions). The histopathological result was as follows: tubular-papillary adenocarcinoma metastases, deriving from the gastrointestinal tract or lung.

After the neurosurgical procedure the patient was hospitalized in the department of oncology, in order to determine the primary location of the tumor. Laboratory results (tumor markers), bronchoscopy, colonoscopy, gastroscopy, and abdominal CT were performed. Gastroscopy revealed the presence of a cardial lesion. The histopathology was as follows: tubular gastric adenocarcinoma.

The patient was qualified for chemotherapy-he received three courses according to the DCF scheme (docetaxel + cisplatin + 5-fluorouracil), as well as radiation therapy– palliative teletherapy at a dose of 30 Gy in 10 fractions to the central nervous system (june/july 2011). The patient was then hospitalized in August at the Department of Oncology, where control CT of the head showed no recurrence, or bleeding, and abdominal CT- no signs of tumor inoperability. The decision concerning surgical treatment of the primary gastric lesion was undertaken.

The patient was admitted to the I Department of General and Oncological Surgery, WCC, on September 22, 2012. On admission, the patient complained of visual disturbances, especially of the right eye. No other disturbances were mentioned. Family history- the patients’ mother was diagnosed with melanoma. The physical examination showed no abnormalities. On admission, PET-CT was performed, in order to exclude disease dissemination, and eventually qualify the patient for abdominal surgery. PET-CT was performed on September, 28, 2011 –apart from the cardial lesion (hypodense lesion, 16x13 mm in size with significant 18F-Fluodeoxyglucose accumulation) no other abnormalities were visualized, suggesting the possibility of metastatic lesions (fig. 1). The patient was qualified for surgery. During laparotomy, a cardiac lesion was visualized, infiltrating the greater curvature, 2 cm in diameter, with a palpable ulceration in its center. Intraoperatively, no other abdominal metastatic lesions were observed. Perigastric lymph nodes were macroscopically suspected of metastasis. The patient was subject to total gastrectomy with D2 lymphadenectomy. Gastrointestinal tract reconstruction was performed by means of esophagojejunosotomy by means of the Roux-en-Y method.
The postoperative course was uneventful. The patient was discharged from the hospital in good general condition on the 11-th postoperative day.

The macroscopic histopathological result was as follows: cardiac tumor, 3x1.5 cm in size, and a satellite lesion -0.4 cm in diameter. The proximal border margin amounted to 0.7 cm. The esophagojejunosotomy was without cancer presence (additional margin of 0.5 cm). The microscopic histopathological result was as follows: tubular-papillary adenocarcinoma (intestinal type), pT2, G2, infiltrating the esophagus. Additionally, vascular neoplastic emboli were diagnosed. The 23 investigated lymph nodes were cancer-free. The immunohistochemical HER2 protein expression was labeled as Score=3+.

The patient was referred to the Department of Oncology, Provincial Hospital, where he received during the period between November 2011 and March 2012, five courses of adjuvant chemotherapy, according to the PLFE scheme (cisplatin, calcium folinian, 5-fluorouracil, epirubicin). Control examinations performed in April, 2012 were as follows: gastroscopy without signs of recurrence, intestinal loops and the anastomosis were patent, abdominal ultrasound without abnormalities.

In July, 2012 the outpatient oncological clinic performed computer tomography of the head, which revealed the presence of 4 hypodense metastatic lesions (<8 mm) located in the left occipital lobe. Due to the number of lesions the patient was disqualified from stereotactic radiotherapy. The patient is continuing treatment at the department of oncology. In September, 2012 he began palliative chemotherapy, according to the LF1 scheme (5-fluorouracyl + leucovorin).

**DISCUSSION**

Improvement in the oncological treatment of gastric cancer, as compared to other neoplasms is insignificant. Proper diagnosis is delayed, thus, the 5-year survival period in Western Europe ranges between 15 – 25% (in Japan-60%), in case of metastatic lesions < 5%, while peritoneal dissemination during initial laparotomy is observed in 15-50% of subjects. Patients with stage III gastric cancer live an average of 6 months, since diagnosis, while those in stage IV – 3 months. The slow progress in chemotherapy is responsible for the slight improvement in therapeutic results. This is associated with the introduction of new therapeutic schemes, based on platinum derivatives, fluorouracil, and epirubicin, both in case of adjuvant therapy, and the more and more common preoperative chemotherapy. In addition, the use of new generation biological agents, such as trastuzumab (ToGA Trial), statistically and significantly improved survival in case of patients with local unresectable and metastatic lesions (13).

Treatment of patients with stage IV gastric cancer is a major challenge. In the absence of clear guidelines considering therapy, each case requires individual analysis and a multidisciplinary approach. Even up to nearly 50% of symptomatic patients, due to the localization of the primary tumor (vomiting, bleeding, perforation, obstruction) require surgical intervention, endoscopic management, or interventional radiology. Chemotherapy alone is usually insufficient, considering palliative therapy- despite the high response rate, rapid
resistance is observed, as well as long-term side effects. In case of some patients with good response to treatment one may observe the “downsizing” of the lesions and potential tumor unresectability. In case of successful perioperative chemotherapy, surgery is considered as adjuvant therapy. The palliative resection of stage IV gastric cancer improves the patients’ quality of life (objectively, according to the QLQ-C30 questionnaire), eliminating cancer symptoms (14, 15), prevents complications, and according to some publications prolongs survival (16, 17). However, there are no prospective, randomized trials concerning the problem. Palliative procedures are often technically demanding and generate hospital costs. The percentage of complications in case of R0 operations is similar to that observed in case of radical procedures, significantly increasing after non-radical macroscopic resections (R2) (14, 15).

Currently, there is no consensus concerning the qualification guidelines for the resection of gastric cancer metastases. Treatment depends on the synchronicity of the lesions, their number, histopathological result of the primary tumor, peritoneal cavity cytology, or radicalism of the primary resection. One should also consider the therapeutic options used by the patient, and current status of the disease in imaging studies (CT and PET-CT of largest value). Most publications mentioned the resection of liver metastatic lesions. However, many authors underlined the statistically significant improvement considering survival in case of resection of isolated metastatic lesions (18).

In the presented case the situation was different. The diagnostic process began with the emergence of central nervous system symptoms, and resection of metastatic lesions of unknown origin. Such patients presented with the following neurological symptoms: lateralization disturbances, increased intracranial pressure (headaches, vomiting), and balance disorders. Less frequently one may observe psychiatric symptoms, confusion, vision disturbances, and seizures (7, 19).

The incidence of brain metastases in patients with gastric cancer is increasing, due to the above-mentioned factors. Most patients are subject to diagnostics after the onset of neurological symptoms. However, improvement in radiological techniques leads to the diagnosis of asymptomatic patients. It is believed that contrast MRI is the method of choice when suspecting CNS metastatic lesions, due to its higher sensitivity and specificity, as compared to other imaging examinations. Computer tomography is widely used, due to its availability and lower costs (20).

Considering the study published by Berlet et al., 46% of patients were diagnosed with isolated brain metastases from gastrointestinal carcinomas, while 54% with multiple lesions. In case of isolated metastasis the lesions were observed most often in the cerebellum (54%), parietal lobe (23%) and frontal lobe (15%). Multiple lesions were found in the supratentorial area – 64% of patients, while in the infra- and supratentorial area – 16%. Berlet et al. observed that the cerebellum localization of the lesion is much more common in case of tumors originating from the gastrointestinal tract, as compared to other neoplasms (21). York et al. also noted a higher incidence of multiple metastases in case of patients with primary gastric cancer (7).

Considering an analysis of 916 patients with brain metastases, 10 (1%) were diagnosed with gastric adenocarcinoma. In 50% of cases the primary lesion was located in the gastric cardia (8, 21). Considering American literature data, which analysed 3320 patients with gastric cancer, brain metastases were observed in 24 (0.7%) cases. In most patients the tumor was located in the proximal part of the stomach (67%) (7, 8). In both of the above-mentioned studies one must point to the more common incidence of brain metastases in case of patients with proximal gastric cancer. The reason of the above-mentioned is unclear. It is possible that the biological differences and metastatic mechanisms are responsible for the

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<th>Type of therapy</th>
<th>Average survival rate (weeks)</th>
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<td>York et al. (7)</td>
<td>Steroids</td>
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<td>WBRT + steroids</td>
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<td>Kaskura et al. (9)</td>
<td>WBRT+SRS</td>
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<td>Surgery+ WBRT</td>
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WBRT: wholebrain radiotherapy
SRS: radiochirurgia stereotaktyczna
above-mentioned. This thesis may be supported by the fact of a worse prognosis in case of patients with proximal gastric adenocarcinoma, as compared to it middle and distal sections (7, 21, 22, 23).

Kasakura et al. noted 11 cases of gastric adenocarcinoma brain metastases from a total of 2322 (0.47%) patients, with the simultaneous dissemination to the bones (46%), liver (42%) and lungs (29%) (7, 8, 9). The above-mentioned Authors reported that patients with lymph nodes and other organ metastases should particularly be monitored for the presence of metastatic lesions to the brain (9).

Neoplastic dissemination to the brain is associated with poor prognosis (24). Treatment is difficult and is not always possible, due to the patients’ general condition. Currently, there is no therapeutic scheme that would provide long-term survival, and significantly improve the patients’ neurological condition (7). Based on the reports published by York et al. and Kasakura et al. patients were divided into three groups, in terms of the obtained therapy (8).

Improvement of the neurological condition was observed in 16.7 % of patients subject to surgical and WBRT treatment or only WBRT therapy (7).

Lee et al. demonstrated that surgical management of brain metastases or stereotactic radiosurgery prolong survival (186 days), as compared to WBRT (136 days) and palliative therapy (26 days) (25).

All patients with stage IV gastric cancer should be subject to multidisciplinary oncological treatment, regardless the resectability of the lesion. According to the presented studies, aggressive therapy (surgery with radio- and chemotherapy) should be proposed to all patients in good general condition, those that are young, and those with limited cancer disease. Resection in such patients might prolong survival and improve their quality of life (7, 8, 9, 12, 25).

REFERENCES


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