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The Radiological Image of the Spread Gastric Cancer to the Nervous System in Patient with Presence of HER-2 Overexpression

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Abstract

Metastases to the brain and spinal cord meninges concern 4-15% of patients with solid tumors. The most frequently occur intracranial in the course of hematological malignancies, lung and breast cancers and predict poor prognosis. Leptomeningeal metastases (LM) are usually a late complication of malignancy occurring from six months to three years after diagnosis of primary tumor. The median survival time of patients with dissemination into meninges is approximately two months; that period is the longest in the patients with breast cancer (79 days).

Keywords: Tumor; Diagnosis; Cancer

Introduction

LM from gastric cancer are very rare, especially among young people. Defined prognostic factors for the involvement of leptomeninges in this group of patients are: Age, performance status, clinical manifestation of the involvement of meninges, cerebrospinal fluid (CSF) block, the time from diagnosis of cancer to dissemination into brain and spinal cord meninges, the type of primary tumor. In recent years, attention has been paid to a new potential prognostic factor: overexpression of HER-2 in subjects with gastric carcinoma, although the results of trials are not conclusive [1]. It is suggested that-as in the case of breast cancer-the presence of HER-2 overexpression in patients with gastric cancer may determine aggressive behavior of the disease including high risk of spreading to the central nervous system. This presentation relates to the case of a young patient suffering from a rare type of gastric carcinoma with HER-2 overexpression and dissemination into meninges, who-despite intensive systemic and radiation therapy-died within 7 weeks from the diagnosis of cancer dissemination to leptomeninges.

Case Presentation

A 37-year-old man with gastric adenocarcinoma (alfa-feto-protein, AFP-secreting, HER2-positive) spreading to the liver and lymph nodes of the abdomen, was admitted in May 2013 to the Department of Radiotherapy and Chemotherapy in order to initiate systemic therapy (cisplatin, fluorouracil and trastuzumab) with further continuation of biological treatment. Partial response to treatment, with decrease in AFP level from 9,000 IU/ml to 150 IU/ml was obtained. After 10 months, new metastatic lesions appeared in the mediastinal lymph nodes, so the next lines of chemotherapy was given: 4 cycles of DCF (docetaxel, cisplatin, fluorouracil) and 4 cycles of EOX (epirubicin, oxaliplatin, capecitabine). There was no response to treatment. In January 2014, the patient experienced a generalized epileptic seizure; therefore, diagnostic neuroimaging was applied; it revealed multiple intracranial metastatic lesions also involving the leptomeninges (Figure 1).

Valproic acid was applied; radiotherapy was applied to the brain area with a fractional dose of 4 Gy to the total dose of 20 Gy followed by irinotecan therapy. In March 2015, pain occurred in the cervical spine area and that was soon followed by gait disturbances and dysuria. Neurological examination revealed lower limbs paresis (3 points on the Lovett scale, with decreased muscle tone), weakened superficial sensibility in the area of perineum. Magnetic resonance imaging (MRI) of the cervical and thoracic spinal cord segment revealed numerous micronodular metastatic lesions on the surface of the cord, measuring up to about 5 mm. MRI of the spine in the lumbar segment showed massive spread of neoplastic process on the surface of the terminal part of cord and into the structures of the cauda equina (Figures 2 and 3). The patient died before the 7th week of diagnosis of dissemination into the leptomeninges.

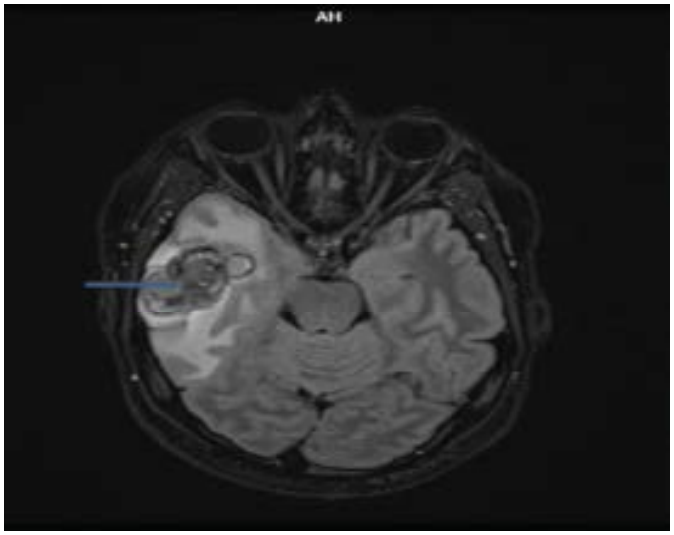

Figure 1: MRI of the head: Metastatic lesion with local edema in right hemisphere.

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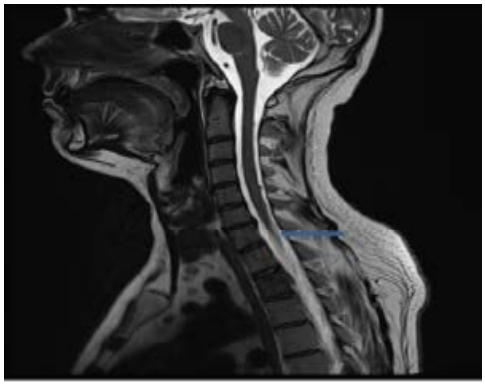

Figure 2: MRI of the of cervical spine: Leptomeningeal metastases.

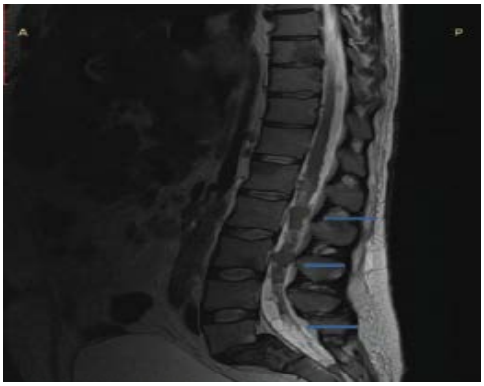

Figure 3: MRI of the spine: Metastases disseminated in the thoracal and lumbal parts of spine and cauda equina.

Discussion

LM are diagnosed on the basis of clinical symptoms, neuroimaging results (brain and spinal gadolinium-enhanced magnetic imaging, Gd-MRI) and tests of CSF. A distinctive feature of the involvement of leptomeninges is the multi-level presence of symptoms related to the brain, cranial nerves, nerve roots and the spinal cord. In the present case, the earliest symptoms were those related to the cerebral cortex with an epileptogenic focus, later followed by clear signs of multilevel involvement of the structures of the spinal canal. According to the observations of other researchers, symptoms of secondary involvement of the leptomeninges in the spinal canal most often include: paraparesis/paralysis of the lower limbs (78%), paresthesia (10%), radiculalgia (25%), and sphincter disorders (2%). The sensitivity of Gd-MRI in the diagnosis of LM is estimated at 66-71% [2]. Most frequently the diagnosis relates to tumor in the subarachnoid location, contrast enhancement of the ependyma and neoplastic nodules involving the cauda equina. Demonstration of the presence of neoplastic cells in CSF is an important diagnostic step; however, in as many as 10% of patients these cannot be found even in a three-fold examination. In the case presented here, MRI results clearly pointed to the spread of neoplastic disease, so CSF examination was abandoned. Peeled-off tumor cells are transported by the flow of CSF to various parts of the neural axis, including the cauda equina, where they tend to settle by the force of gravity and slow CSF flow. The presence of LM causes neurological disorders as a result of: demyelination followed by axonal degeneration; bloodstream disorders in the circulation system and/or CSF flow disorders.

The spread of gastric carcinoma into the central nervous system is very rarely reported (<1% of patients in this group) [3]. Interestingly, every 4th patient in this group revealed overexpression of HER-2; in those cases, rapid progression of the disease was observed. HER-2 (human epidermal growth factor receptor-2) is a tyrosine kinase receptor encoded by ERBB-2 on chromosome 17. It belongs to the HER family of proteins whose expression is found in many tissues, including the breast, gastro-intestinal tract, kidneys and the heart. By assisting in the processes of proliferation and suppression of apoptosis, it facilitates uncontrolled cell growth and tumorigenesis. Overexpression of HER-2 is present in up to 30% of patients with breast cancer (HER-2 positive subtype), which is associated with a higher risk of local recurrence and dissemination [4]. The developments in molecular biology and improved accessibility of genomics research allow us to evaluate the importance of HER-2 overexpression also in patients with other malignancies, including gastric carcinoma. HER-2 overexpression or amplification is observed in 9-26% of patients in this group, which may be related with more aggressive course of the disease and a less typical location of metastases including brain or leptomeninges. However, the opinions of other researchers on the importance of HER-2 as an adverse prognostic factor are divergent [4,5].

Conclusion

LM should be considered in any patient with cancer, particularly when the neurological symptoms occur in a few different sites on the neural axis. Special diagnostic attention in this regard is required with patients with HER-2 overexpression which increases the risk of cancer dissemination, and which is consistent with the observations of other authors and the clinical case presented here. Determination of the actual role of HER-2 overexpression in patients with gastric carcinoma may contribute to the development of a diagnostic algorithm which would account for neuroimaging during the asymptomatic phase of the disease in the nervous system and for neuro-radiotherapy at an early stage of the disease.

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