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Case Report

A Case Report of Atypical Presentation and Management of the Leptomeningeal Carcinomatosis

Zlatko Hucika[1]*, J Hucika[2], M Oštrić[3] and I Ravlić[4]

[1]Department of Neurology, General Hospital Zabok and Hospital of Croatian Veterans, Zabok, Croatia

[2]Department of Internal Medicine, Special Hospital for Prolonged Treatment Duga Resa, Duga Resa, Croatia

[3]Department of Internal Medicine, General Hospital Zabok and Hospital of Croatian Veterans, Zabok, Croatia

[4]Department of Radiology, General Hospital Zabok and Hospital of Croatian Veterans, Zabok, Croatia

***Corresponding Author:** Zlatko Hucika, Department of Neurology, General Hospital Zabok and Hospital of Croatian Veterans, Zabok, Croatia.

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Abstract

Leptomeningeal carcinomatosis represents metastatic spread of various malignancies into the envelopes of the brain and the spinal cord. The most common origin of this type of carcinomatosis are haematological tumors, breast and lung cancer. The typical initial presentation of this condition consists of neurological symptoms that originate in the brain (headache, ataxia and seizures), cranial nerves (diplopia, peripheral facial palsy and trigeminal nerve dysfunction), and spinal nerves (muscle weakness, back and limb pain, sphincter dysfunction and sensor neural symptoms). Our case represents a patient who presented with a variety of symptoms (loss of appetite, weight loss and depression) so leptomeningeal carcinomatosis initially was not listed as a differential diagnosis. A 69-year-old woman was admitted to the gastroenterology ward due to malaise and weight loss. Five months prior to admission she experienced mood changes and poor appetite. The initial tests included laboratory tests, upper and lower endoscopies, chest x-ray and gynaecology referral and no abnormalities were found apart from slightly raised tumour markers Ca 125, CEA and Cyfra 21-1. At the time patient was showing lack of interest in her surroundings and psychiatry referral was sent. Psychiatrist suspected that the weight loss and loss of appetite were caused by depression and patient was discharged. She was re-admitted three months later, this time with mostly neurological symptoms: headache, sleepiness, neck stiffness, right-sided weakness, vomiting and multiple cranial nerves palsy. MSCT of the head showed nonspecific atypical hyperdensity of vermis in cerebellum and gadolinium-enhanced MRI of the brain and spinal cord was performed showing abnormal T1 postcontrast enhanacement changes on the brain convexities and cervical spinal cord. At this time leptomeningeal carcinomatosis was included in the differential diagnosis. Cerebrospinal fluid analysis was performed showing cancer cells, most probably originating in the lungs. MSCT scan of the chest confirmed the diagnosis of lung malignancy and MSCT scan of the abdomen and pelvic area was insignificant. Unfortunately patient has died before diagnostic process could be finished. This is an example of a rare initial presentation of the leptomeningeal carcinomatosis which included psychiatric symptoms and without typical initial neurological symptoms.

Keywords: *Leptomeninegal Carcinomatosis; Psychiatric Symptoms; Lung Carcinoma; Cerebrospinal Fluid; Non-Small Cell Lung Cancer; Epidermal Growth Factor Receptor Mutations*

Introduction

Leptomeningeal carcinomatosis (LC) represents a devastating spreading of metastatic cancer (mostly solid) in the central nervous system (CNS) with a poor prognosis and a survival rate of approximately 4 months [1]. This is due to late-stage diagnosis of systemic cancer. Survival rate may vary and be prolonged due to high Karnofsky Performance Status (KPS) above 70 or Eastern Cooperative Oncology Group Performance Status (ECOG PS) above 0-1, with earlier diagnose and with controlled systemic disease, type of treatment, younger age of the patient, no focal neurological deficits, a slightly change of the cerebrospinal fluid (CSF) [1-5]. Generally, all malignant tumors could cause LC with both possible manifestations- solid tumor deposits or diffuse dissemination [6]. Regarding epidemiology, LC

is detected in both-solid tumors (most frequent breast cancer, lung cancer and melanoma) in 5 - 8% of cases and haematological (leukaemia and lymphoma) in 5 - 15% of cases [7-10]. In rare cases it might be accompanied with primary brain tumors in 1-2% of cases (e.g. gliomas, ependimomas, medulloblastomas etc.) [11]. One small, but quite interesting study about seasonal variability showed significant increase of LC incidence in the summer time [12]. Most common presenting symptoms are cerebral (headache, ataxia, mental change, seizures), cranial nerve lesions (diplopia, peripheral facial palsy, trigeminal nerve disfunction etc.) and spinal (limb weaknes, back and limb pain, sphincter disfunction, sensory nerve symptoms, etc.) [13]. The prevalence of mental changes in LC varies in studies (17 - 52%), but without specifying in what stage of the disease they onset [14-17]. We report a case of leptomeningeal carcinomatosis in a patient with atypical initial presentation of psychiatric symptoms only.

Case Presentation

A 69-year-old woman, non-smoker, with no significant illness in her medical history except arterial hypertension, was admitted twice to a General Hospital (Department of Internal medicine, Gastroenterology) due to general weakness, low appetite and weight loss. Five months prior to the admission she started to have symptoms of slight mood disorder and poor appetite. She underwent a wide diagnostic procedure process (laboratory analysis, gastroscopy, colonoscopy, radiographyc scan of the lungs) without any abnormality found. An abdominal ultrasound showed 2 smaller hepatal hemangiomas which was also seen at the multisliced computorized tomography (MSCT) of the abdomen. There was no significant finding in the pelvic area with same diagnostic method. Three tumour markers were raised, a cancer marker 125 (Ca 125) was moderately raised, carcinoembryonic antigen (CEA) and cytokeratin 19 fragments (Cyfra 21-1) were slightly raised, others (cancer antigen 15-3/Ca 15-3 and cancer antigen 19-9/Ca 19-9) were negative. Laboratory blood analyis showed slightly low folate and D vitamin levels. The substitution of folate and vitamin D has been given but without any change of clinical state. The gynecologic diagnostic procedure has been provided too, with a negative results. As the psychiatric symptoms were progressive with loss of social interest, the psychiatrist has been consulted about a suspected depressive disorder and the weight loss has been attributed complications of the above mentioned state. After 3 months the patients clinical state became worse. During a second hospitalization at the Department of Internal medicine, she finally developed more specific neurologic signs. She started to suffer of headaches with somnolence, neck stiffness, multiple cranial nerve disorders, vomiting, ocular bobbing and right-side hemiparesis. A neurology specialist has been consulted with a noncontrast MSCT of the brain. There was nonspecific atypical hyperdensity of the vermis, non consistent of parenhymal haematoma, without its clear ending of the rest of parenhyma without other patologic changes. Therefore, she was immediately transferred to the Department of Neurology for further diagnostic procedure. She underwent magnetic resonance imaging (MRI, 1.5 Tesla) of the brain and cervical spine with a contrast as the next step. The MRI (T1 sequence with gadolinium) showed pial gadolinium enhancement and nodularity, typically over the cerebral convexities, in the basal cisterns, on the tentorium and the spinal cord of the cervical region (Figure 1 and 2, lesiones are arrow pointed). Further, we performed a lumbar puncture and took cerebrospinal fluid (CSF) for basic liquor analysis. We found slightly xanthous liqour with 500 erithrocytes in it, mild pleocytosis (28 of leukocytes), hypoglycorrhachia (1.2 mmol/L) and atypical epithelial cells in it. There was no possibility for differentiation of white blood cells and immunocytological analysis in liquor at our hospital. In differential diagnosis we suspected neurotuberculosis as well, but the PCR testing in liqour was negative. The LC matched better with clinical presentation. We suspected for cancer cells in CNS also, so we sent the additional samples in the clinical hospital for a several types of analysis. A single examination confirmed basic patologhic findings (as those one in our hospital), but the most important finding was the positive morphologic and immunocytologic analysis corresponding to the adenocarcinoma; most probably of lung origin. Others patologhic findings were high values of protein S100, neuron-specific enolase (NSE) and b2-microglobuline. There wasn`t available equipment for measuring opening pressure but clinical signs of increased intracranial pressure (headache, alteration of consciousness, vomiting) had been present. In accordance with above mentioned, the fundus examination showed papilledema. We set up the diagnosis of LC.

Next, the patient underwent a MSCT of the thorax, abdomen and pelvic area which showed a solid nodule with spiculated margins (27 mm in longest diameter) in the right apical segment of the lung that was suspected for a tumour and with description of lung lymphangiosis. In meanwhile, the patient rapidly became worse clinically and neurologically just few days after transfer to our Department. She developed cerebral comma with letal outcome at the end. We didn't consult a neurosurgeon because the family was reluctant to neurosurgical treatment. Unfortunately, there was no time left to consult a pulmologist and oncologist for further diagnostic and therapeutic options.

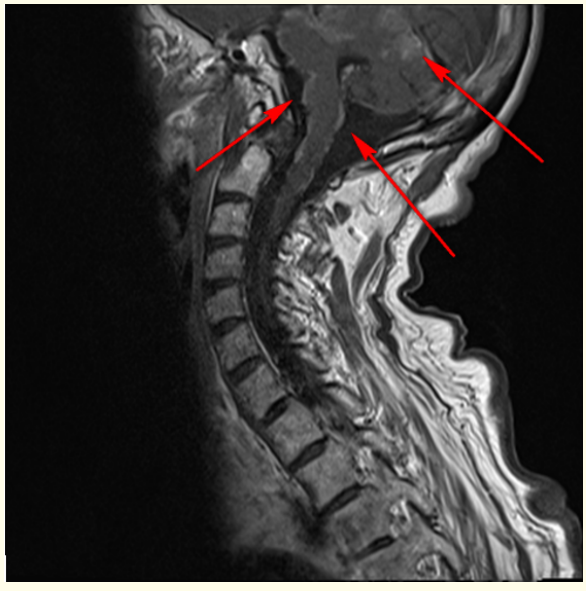

Figure 1*: Sagittal T1 postcontrast MRI abnormal enhanacement shadow (arrow pointed).*

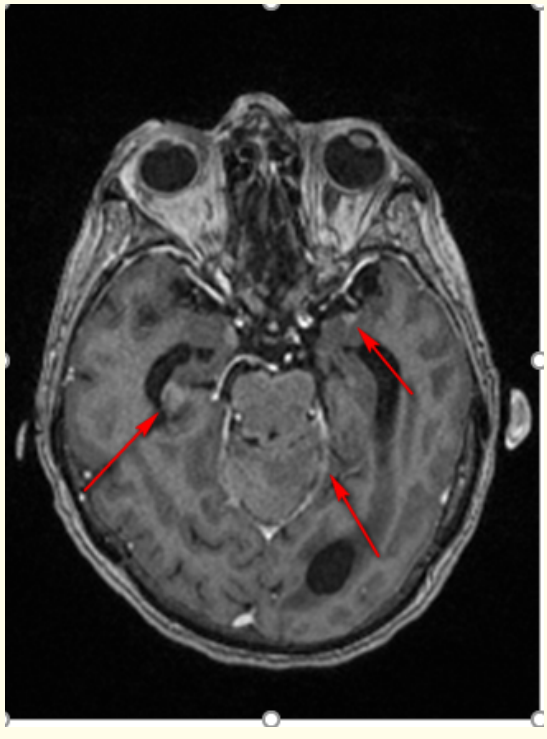

Figure 2: *Axial T1 postcontrast brain MRI abnormal enhanacement shadow (arrow pointed).*

Discussion

Leptomeningeal carcinomatosis (LC) is a serious consequence of primary systemic cancer as a result of malignant cell dissemination. Our major focus in this discussion will be diagnostic and therapeutic options in patients with LC due to lung carcinoma because we have

the opinion that our patient was such a case.. At the time the diagnose was set up, the patient was in a rapidly progressive stage. In our case we didn't have enough time to proceed with a further diagnostic procedure and evaluation for seeking potential therapy. In 2017. the Leptomeningeal Assessment in the Neuro-Oncology (LANO) Group and the European Association for Neuro-Oncology/European Society for Medical Oncology (EANO/ESMO) have proposed guidelines for diagnosis, treatment and follow-up of patients with LC orringinated from solid tumors in clinical practice [3,18]. When typical clinical symptoms and/or signs appear in a patient with a tumor we should consider LC as differential diagnosis [13,18].

Regarding neuroimaging, cerebrospinal MRI is a technique of choice. It has to be done with gadolinium enhancement (at least 1.5 Tesla field strenght) [19]. The neuroradiologists use standard sequences, but contrast-enhanced T1-weighted spin-echo images are a better choice than FLAIR images (34% vs 66% of sensitivity) [20]. Brain MSCT has poor senstivity of only 30% [1]. Most common findings in cerebrospinal MRI are sulcal enhancement in cerebral hemispheres, linear ependymal area, nerve roots and cauda equina. A CSF flow abnormalities were described up to 70% such as hydrocephalus, also [22,23]. The sensitivity and specificity is relatively high, 66 - 98% [13,20,21]. It`s recommended to do a cerebrospinal MRI before CSF diagnostic or ventricular shunt placement because we can get a false positive results of meningeal contrast enhancement [18]. Next, 18F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET- CT) might be done, but it is not so useful and available in everyday practice. A recent small study suggests a potential role of metabolomic approach (measuring myo-inositol, creatin, lactate and citrate) of brain MRI spectroscopy in setting of accurate diagnosis with sensitivity of 92% and specificity of 96%, and even in grading of LC in patients with lung carcinoma [24].

Analysis of CSF and identification of tumor cells is the gold standard and vital for diagnosis of LC. The sensitivity is not so high; about 60%, sometimes even 95%, but it mostly depends to the number of CSF analysis taken, most common after 3 high-volume lumbar punctures, but specificity is more than 95% [10,25,26]. In some particular cases the flow cytometry has to be done (e.g. hematologic malignancy). Also we can find proteinorrhachia, pleocytosis, hypoglycorrhachia and increased open pressure. Tumor cells or atypical cells will undergo immunocytochemistry. A wide number of tumor-specific CSF biomarkers has been used for LC screening such as neuron-specific enolase (NSE), ß-glucoronidase, lactate dehydrogenase, standard carcinoma markers and some others molecules regarding angiogenesis [18]. Some novel tehniques has been investigated recently, such as tumor marker immunofluorescence in situ hybridisation (TM-iFISH), epithelial cell adhesion molecule antybodies (Ep-CAM), CellSearch technology or detecting a genomic alteration by PCR method but with limited data with a need for further validation and higher number of patients in future studies [27-31]. Detecting of epithelial growth factor receptor mutations (EGFR) in CSF could be helpful to determine specific therapy in patients with lung carcinoma [32,33].

Although rarely indeed, leptomeningeal biopsy might be done as an alternative in cases of negative repeated CSF analysis if we still have suspicions for LC. Future possible improved diagnostic tools such as microarrays, real-time polymerase chain reaction (qPCR), whole exome sequencing and detecting circulating tumor DNA (ctDNA) in CSF known as „liquid biopsy“ are still tested [33,57-60]. The EANO/ESMO has also proposed a classification based on verified citology or hystology positive findings (type I) or negative findings (type II) and neuroimaging findings as linear (type A), nodular (type B), both (type C) and neither or only hydrocephalus seen in neuroimaging (type D) [18]. The classification mentioned above could serve as a guidance for who and when to treat.

Regarding treatment, there is no cure for LC to date, only intention to prolong survival and preserve the best possible life quality. Several modalities ore therapy options are proposed and sugested by expert opinion or low number case series, without available randomized wide number double controlled studies [18]. In LC with non small cell lung carcinoma (NSCLC) some platinum–based agents (paclitaxel, gemcitabine, pemetrexed) can be given [34,35]. The vast majority of systemic chemotherapeutics (methotrexate (MTX), cytarabine, capecitabine, thiotepa and temozolamide) are effective for primary, systemic neoplasms, poorly penetrate in CNS through blood brain barrier (BBB) but it should be consider for vast majority patients with type B/C of LC [18,43]. Ventriculoperitoneal shunting could be considered as symptomatic treatment of hydrocephalus and for intratecal therapy in selected patients. Intratecal chemotherapy is considered the mainstay treatment in LC, most common MTX, cytarabine and thiotepa [1]. It is useful to do a CSF flow study with radioisotope before application [56]. Application is preferred via intraventricular catheter rather than repeated lumbar puncture and should be considered in type IA/C LC but it has some limitations (contraindicated in hydrocephalus, risk of infection, neurotoxicity) [18]. Both, systemic and

intratecal chemoterapeutics have poor results regarding prolonged survival [16]. Focal radiotherapy (FRT) could be used to treat type B LC, sometimes in cranial nerve palsies or cauda equina syndrome after exclusion other causes or even to help to relieve brain CSF obstruction in 50%, or spinal obstruction in 30% of cases [18,45]. An alternative, a whole brain radiotherapy (WBRT) have no clear association with prolonged survival in all patients except some selected one such the one with EGFR mutations, but it still should be considered in extensive forms of LC as a palliative treatment [38,46,56]. Patients with detected spinal lesions are candidates for focal radiotherapy in providing palliative relief [55]. However, one should always have in mind the side effects such as bone marrow toxicity, dermatitis, enteritis etc. Nowadays, a numerous other agents have been tested in patient with NSCLC such as recombinant monoclonal antibody targeting VEGF (bevacizumab), EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, afatinib, osimertinib, cetuximab, icotinib), anaplastic lymphoma kinase (ALK) inhibitors (crizotinib, alectinib), anti-programmed cell death 1 (PD1) agents (nivolumab, atezolizumab, pembrolizumab) [36-42,54]. There are several single case reports or multicentric studies about possible better therapeutic response of above mentioned novel agents, depending what receptor mutation type it is about and some of them suggest a combination of a dual therapy [49-53].

Survival rate in lung carcinoma in a period of 6 months is 48% and of 1 year is 19%, respectively [46,47].

At the time the diagnosis of LC is set up initial clinical/performance status is the most important factor in prognosis; those with ECOG score 0 - 1 (match KPS ≥ 70 score) have better chance than others with ECOG score ≥ 2 (match KPS ≤60 score) [47]. Others factors regarding better survival rate are younger age (under 60), type of primary tumor and its site of progression, combined modality treatment, controlled intraventricular pressure, CSF responses to treatment [44,47,48]. At the follow up it is recommended to use clinical, neuroradiological or CSF study (if CSF chemotherapy was administrated) reevaluation every 2 - 3 months or earlier if needed [18]. The main goal is to prolong survival and preserve the best possible life quality.

Conclusion

We are not surprised that the LC in our case was not recognized at first, because of the lacking of typical symptoms and the atypical clinical presentation at start (mild mood disorder and poor appetite). We think it is important to highlight LC as a differential in a patient with psychiatric symptoms as an initial and single presentation at the beginning. The limitation of this article is in the lack of early recogntion of the diagnosis and possibility of trying to prolong survival with best quality of life. Also, we couldn't confirm the origin of the cancer cells in the liquor due to lack of time for it, only indirectly suspect of lung carcinoma. Treatment of LC with EGFR TKI, cytotoxic chemo-therapy or WBRT in selected patients is associated with relative prolonged survival period. To date, intrathecal therapy still represents the main type of treatment in LC, but still there is no standard therapy that is evidence based.

Disclosure

The authors report no conflict of interest.

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