Uma Forma Rara de Apresentação de Carcinoma Gástrico com Carcinomatose Leptomeníngea e Síndrome de Secreção Inapropriada de Hormona Antidiurética: Caso Clínico

Rare Presentation of Gastric Cancer as Leptomeningeal Carcinomatosis and Inappropriate Antidiuretic Hormone Secretion Syndrome: Case Report

Inês SF da Silva[1], Ryan Costa Silva[1,2], Mariana Cerejo Silva[1], Sofia Reimão[3,4], Lígia Peixoto[1,2]

Resumo:

Carcinomatose leptomeníngea e síndrome de secreção inapropriada de hormona antidiurética (SIADH) paraneoplásica são raros em neoplasias gástricas, principalmente como manifestação de neoplasia gástrica assintomática.

Mulher, 87 anos, admitida por diminuição da reatividade a estímulos externos, alterações mnésicas, desorientação e redução da autonomia por instabilidade da marcha com 20 dias de evolução. O estudo analítico era sugestivo de SIADH, a tomografia computorizada (TC) tóraco-abdómino-pélvica mostrava adenopatias no pequeno epíploon, e o liquor tinha proteinorráquia e hipoglicorráquia. A endoscopia alta mostrou lesão ulcerada da *incisura angularis*. A doente evoluiu desfavoravelmente com hidrocefalia e crises epiléticas. A RM crânio-encefálica foi sugestiva de carcinomatose leptomeníngea e a biópsia gástrica mostrou carcinoma pouco coeso, em parte de células em anel de sinete. A pesquisa de células neoplásicas no líquor foi positiva (carcinoma). Faleceu sem possibilidade de terapêutica dirigida.

Os autores pretendem salientar a possibilidade de carcinomatose leptomeníngea e SIADH como formas raras de apresentação de carcinoma gástrico.

Palavras-chave: Carcinomatose Meníngea; Neoplasias do Estomago; Síndrome de Secreção Inadequada de HAD.

Abstract:

Leptomeningeal carcinomatosis (LC) and paraneoplastic syndrome of inappropriate antidiuretic hormone secretion (SIADH) are rarely associated with gastric cancer, especially as presenting forms of asymptomatic gastric cancer.

An 87-year-old woman was admitted because of lethargy, mnesic deficit, disorientation and gait instability affecting her autonomy for 20 days. Laboratory tests were suggestive of SIADH, body computed tomography (CT) scan showed lymph nodes near the lesser omentum and cerebrospinal fluid showed elevated protein and low glucose. Gastroscopy revealed an ulcerated lesion at the *incisura angularis*. She had a rapid unfavourable outcome with hydrocephalus and recurrent seizures. Head magnetic resonance imaging scan was suggestive of LC and gastric biopsy showed poorly cohesive carcinoma with some signet ring cells. Neoplastic cells in cerebrospinal fluid were positive and compatible with carcinoma. The patient died without any possibility of treatment.

The authors want to emphasize the possibility of LC and SIADH as rare presenting forms of gastric cancer.

Keywords: Inappropriate ADH Syndrome; Meningeal Carcinomatosis; Stomach Neoplasms.

Introduction

Leptomeningeal carcinomatosis (LC) is the multifocal spread of malignant tumor cells along the meninges.[1] It is a rare late complication of tumors[2] and a fatal disease.[3] Its incidence is low, occurring in only 5% of all patients with metastatic solid tumors.[2] Gastric cancer-induced LC is less common,[4] with an incidence of only 0.17%-0.69% among all gastric cancers.[1] However, LC as the initial manifestation of asymptomatic gastric cancer, is extremely rare.[4]

SIADH is a syndrome associated with inappropriate secretion of serum antidiuretic hormone (ADH) in the absence of plasma hypotonicity[5] resulting in excessive water reabsorption in the collecting ducts6 and hypoosmotic and euvolemic hyponatremia.[7] It occurs in 1%-2% of all patients with malignant tumors,[7] most commonly in patients with small cell lung cancer, and has been reported in 3% of patients with head and neck cancer.[8]

[1]Serviço de Medicina Interna – Área B, Unidade Local de Saúde Santa Maria, Lisboa, Portugal
[2]Clínica Universitária de Medicina Interna da Faculdade de Medicina da Universidade de Lisboa
[3]Serviço de Imagiologia Neurológica, Unidade Local de Saúde Santa Maria, Lisboa, Portugal
[4]Clínica Universitária de Imagiologia da Faculdade de Medicina da Universidade de Lisboa

https://doi.org/10.60591/crspmi.188

SIADH has also been identified in patients with other solid tumours but at lower rates than in small cell lung cancer or head and neck cancer.[8]

Case Report

An 87-year-old woman was admitted with waxing and waning mental status changes (she was lethargic on the day of admission), mnesic deficit, disorientation and unsteady gait affecting her autonomy that had started 20 days earlier. She had no headache, fever, nausea, vomiting or weight loss. She had been admitted to the emergency department (ED) 20 days earlier for adynamia, anorexia, bilateral lower limb weakness and unsteady gait. Until then she was a completely independent 87-year-old woman who took care of her home and family. At that time plasma sodium was 131 mmol/L (reference range (RR) 135-145) and plasma osmolality was 267 mOsmol/kg (RR 275-295). A body computed tomography (CT) scan was performed at that time and showed only lymph nodes near the lesser *omentum*. She was discharged. She returned to the ED after 20 days because she couldn't walk by herself due to unsteady gait and because she had not regained her previous mental status and autonomic function.

She had hypertension and was treated with losartan 50 mg/day and acetylsalicylic acid 150 mg/day. Because of mainly orthostatic hypotension, she had been treated with deflazacort 6mg/day and midodrine 2.5 mg/day 7 days before admission, after exclusion of hypothyroidism and glucocorticoid deficiency, but without improvement.

Physical examination: disorientation in time and space, speech rather incoherent with paraphasia and perseveration. There was no definite focal weakness and sensory deficit and no meningeal signs. Ocular fundus was unremarkable, retropulsion when in upright position, unsteady gait requiring bilateral help but no ataxia. Blood pressure 123/65 mmHg, heart rate 71bpm, temperature 36.1°C.

ED blood work: plasma sodium 122 mmol/L (RR 135-145), plasma osmolality 251 mOsmol/Kg (RR 275-295), blood urea nitrogen 52 mg/dL (RR 16-49), creatinine 0.74 mg/dL (RR 0.5-0.9), potassium 5 mmol/L (RR 3.5-5.1), c--reactive protein 0.15 mg/dL (RR <0.5). Head CT scan showed chronic small vessel lesions in the white matter. She was treated with isotonic saline because of suspected hypovolemic hyponatremia, and then the patient was admitted to an internal medicine ward for evaluation.

In the medical ward, the patient showed no signs of dehydration or overhydration. Plasma sodium was 130 mmol/L, plasma osmolality was 264 mOsmol/kg. Urine was analysed for euvolemic hypoosmolar hyponatremia (Table 1). She had inappropriately concentrated urine (>200 mOsm/L) (Table 1) and high urinary sodium concentration (Table 1).

As it could be SIADH, she was started on oral fluid restriction. She also had low serum uric acid concentration (2.7 mg/dL (2.4-5.7), normal glucose (114 mg/dL (70-110), normal total cholesterol (181 mg/dL (<190), normal triglyceride (63 mg/dL (<150) and hypothyroidism and glucocorticoid deficiency were excluded. It was necessary to start hypertonic saline to treat SIADH while maintaining oral fluid restriction (Table 1). Finally, a loop diuretic was required to treat SIADH in addition to oral fluid restriction and hypertonic saline to reduce urine osmolality.

A lumbar puncture was also performed because hyponatremia (130 mmol/L) could not fully explain her neurologic symptoms: cerebrospinal fluid (CSF): 6 cells/mm3(<5), protein 180.4 mg/dL (15-45), glucose 15 mg/dL(40-70) for 133 mg/dL plasma glucose (70-110). CSF Gram, acid-fast *bacilli, cryptococcus neoformans* and bacterial smears and cultures were all negative. Polymerase chain reaction for *enterovirus, herpes simplex virus* type I and II, varicella *zoster virus* and *mycobacterium tuberculosis* were also negative. Brain magnetic resonance imaging (MRI) revealed leukoaraiosis consistent with chronic small vessel disease.

Because lymph nodes near the lesser *omentum* were present on the body CT performed at the previous ED visit and SIADH was present without cause, an upper endoscopy was performed. During the endoscopy, a suspicious ulcerated lesion was observed at the *incisura angularis* with a diameter of 3 cm, so a biopsy was performed (Fig. 1).

Table 1: Patient´s blood and urine tests consistent with SIADH.

Parameter	Admission	Isotonic saline and oral fluid ingestion	Isotonic saline and oral fluid restriction	Hypertonic saline and oral fluid restriction
Hemoglobin (g/dL)	14.9 (12-15.3)	13.1 (12-15.3)	13,3 (12-15.3)	14.6 (12-15.3)
Plasma sodium (mmol/L)	122 (135-145)	130 (135-145)	132 (135-145)	127 (135-145)
Plasma osmolality (mOsmol/kg)	251 (275-295)	264 (275-295)	268 (275-295)	258 (275-295)
Urine sodium (mmol/L)		33 – spot urine	53 – 24 h urine 24 mmol/24 h	133 – 24 h urine 219 mmol/24 h
Urine osmolality (mOsmol/kg)		292 – spot urine	597 – 24 h urine	422 – 24 h urine

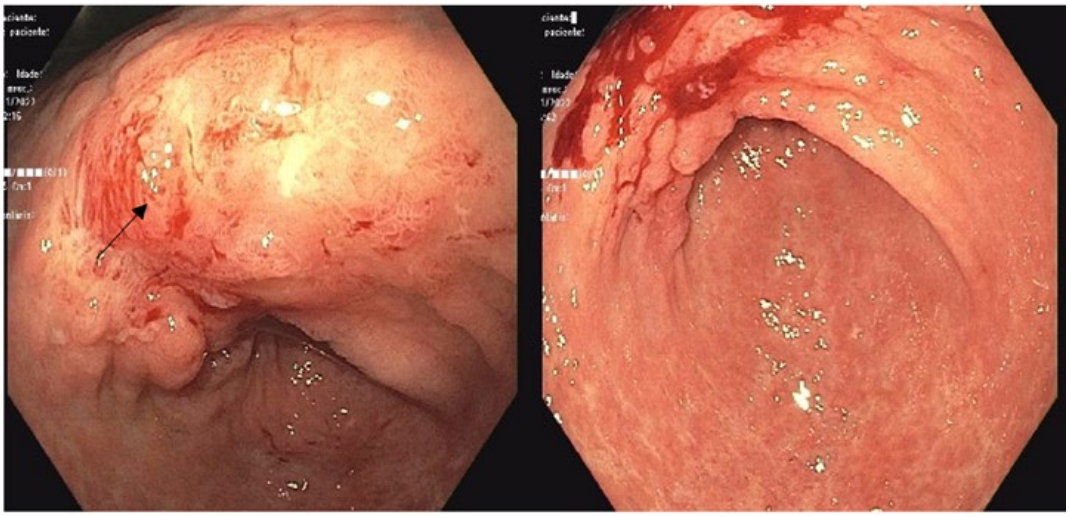

Figure 1: Upper endoscopy revealed an ulcerated lesion at the incisura angularis (left image), which was biopsied (right image).

Her clinical condition worsened with clonic seizures without complete recovery of previous mental status, and she was started on antiepileptic drug. At that time, her sodium level was normal 142 mmol/L (135-145). Brain CT scan showed no ischemic or hemorrhagic lesions but supratentorial hydrocephalus. No surgical indication after neurosurgical consultation. Although there was no diagnosis, tuberculous meningitis was suspected and due to clinical deterioration, she was started on anti-tuberculostatic drugs including rifampicin, isoniazid, ethambutol, pyrazinamide and steroid. Electroencephalogram confirmed the clinical seizures. A second MRI with intravenous gadolinium administration was performed and showed abnormal meningeal enhancement detected by gadolinium-enhanced T1 sequences (Fig. 2) and increased signal in the *sulci* detected by gadolinium--enhanced fluid-attenuated inversion recovery (FLAIR) weighted imaging (Fig. 3), consistent with LC. MRI also showed supratentorial hydrocephalus with transependymal edema and cortical *sulci* effacement.

Cytologic analysis of her CSF was positive for carcinoma and gastric biopsy was compatible with poorly cohesive gastric carcinoma partially with signet ring cells. Anti-tuberculostatic drugs were discontinued. After multidisciplinary discussion, considering her diagnosis (with poor prognosis itself), age, neurological symptoms, and performance status it was decided that best supportive care was the best individualized option to offer. The patient died 3 weeks after admission.

Discussion

Recognition of LC is very important and requires a high index of suspicion.[3] LC is difficult to diagnose, especially as the first sign of a primary tumor,[9] because the presenting symptoms and signs of LC are usually non-specific,[3] and

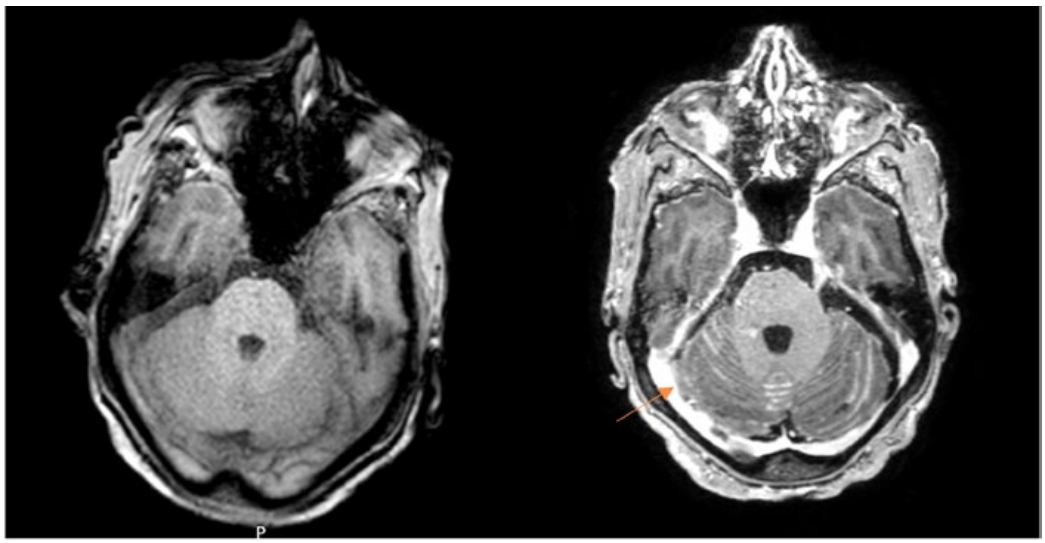

Figure 2: T1 sequence without gadolinium contrast enhancement on the left; Gadolinium-enhanced T1 sequence showing abnormal meningeal enhancement (right image).

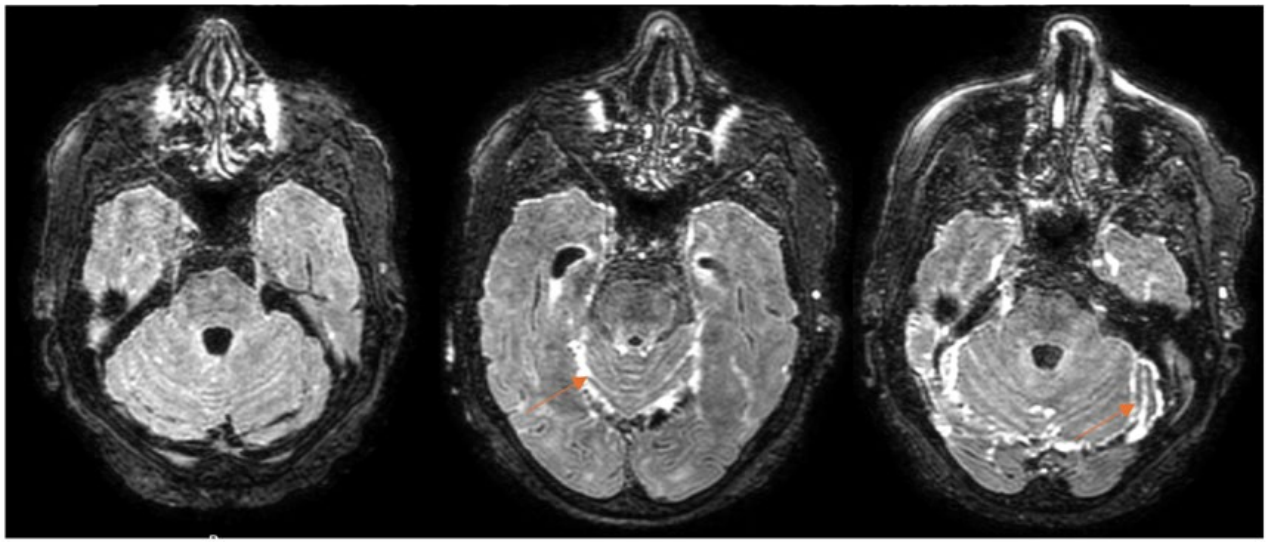

Figure 3: Flair without gadolinium contrast enhancement on the left; 3D Gadolinium-enhanced fluid-attenuated inversion recovery weighing MRI showing increased signal in the sulci (images on the right and center).

because CSF cytology and MRI, which should be used to diagnose LC in patients with suspicious clinical signs[3] have low sensitivities[10] (MRI around 65%–75% and CSF 54%, rising to 91% with repeated sampling)[10]. Clinical manifestations vary and include headache, nausea, vomiting, altered mental status, seizures, weakness, cranial nerve deficits,[10] lethargy, gait disturbance, incontinence, behavioural changes, nuchal rigidity and neck pain,[2] making differential diagnosis difficult.[10] Our patient had lethargy, mnesic deficit, disorientation and unsteady gait at presentation and with the progression of the disease she also had seizures and progressed to coma. She never had headache, which is the most common brain symptom.[3]

She also had hyponatremia (122 mmol/L) at presentation and hyponatremia has also been shown to be associated with significant comorbidities such as gait instability.[5] Common symptoms and signs of hyponatremia also include headache, nausea, vomiting, muscle spasms, lethargy, disorientation, and depressed reflexes[5] and these symptoms are common in LC. She was treated with fluid restriction, hypertonic saline and loop diuretic and the hyponatremia resolved but the symptoms didn't resolve because they were probably related to the LC itself. Hyponatremia is a negative prognostic factor in cancer patients, and it is often caused by SIADH.[8] The presence of SIADH has been associated with a higher propensity for central nervous system metastases, poor response to chemotherapy and advanced stage of cancer.[5] In this case SIADH could be diagnosed because she had (Table 1) hypoosmolar hyponatremia, inappropriately concentrated urine (>200 mOsm/L),[5] high urinary sodium concentration (>40 meq/L),[2] low serum uric acid concentration,[2] normal acid-base and potassium balance,[2] normal renal function[2] and hypothyroidism/ glucocorticoid deficiency were excluded (euvolemic hyponatremia may also occur in these conditions, so they must be excluded)[5]. The patient's hyponatremia was most likely secondary to paraneoplastic SIADH, presumably caused by LC, since SIADH is much rarer when directly caused by gastric cancer. ADH was not measured in plasma or tissues and this is a limitation of the case that only allows us to infer the direct cause of SIADH.

She was started on anti-tuberculostatic drugs as tuberculous meningitis was not ruled out at that time. Guo *et al* 2014[4] also reported a case of LC as the initial manifestation of gastric adenocarcinoma where tuberculous meningitis was suspected and anti-tuberculostatic drugs were administered before the final diagnosis of LC. After the start of anti-tuberculostatic drugs the 2nd MRI was performed and this one had suggestive aspects of LC as abnormal meningeal enhancement and increased signal of the *sulci* detected by gadolinium-enhanced T1 sequences and fluid-attenuated inversion recovery weighing respectively[3] (Fig. 3). The first MRI did not show characteristic aspects of LC which can be explained by its low sensitivity (probably due to the lack of gadolinium contrast enhancement) and interobserver variability. On the other hand, CSF cytology analysis showed carcinoma and the diagnosis of LC was made, as CSF cytology is required for definite diagnosis of LC.[3] Anti-tuberculostatic drugs were then discontinued. Regarding the primary tumour, the patient did not have any gastric symptoms. The CT scan showed only lymph nodes near the lesser *omentum*, so an upper endoscopy was performed. It showed a suspicious ulcerated lesion at the *incisura angularis* with histology compatible with poorly cohesive carcinoma with partial signet ring cells. LC most commonly presents in signet ring cell carcinoma, with multiple metastatic sites and 12 months after initial diagnosis.[9] In fact, our patient's cancer was poorly cohesive carcinoma partially with signet ring cells but it did not present neither with multiple metastatic sites (she only had lymph nodes near the lesser *omentum*) nor 12 months after diagnosis. Instead,

LC was the initial manifestation of asymptomatic gastric cancer, which is extremely rare.[4] After multidisciplinary discussion it was decided that best supportive care was the main goal of care due to the patient's age, diagnosis, neurological symptoms and poor performance status at the time. This is supported by evidence that treatment remains challenging and palliative care is essential,[10] particularly in patients with poor prognostic factors such as age over 50 years, major neurological deficits, high central nervous system disease burden, high CSF protein level,[10] Karnofsky Performance Status <60, extensive systemic disease with few treatment options and encephalopathy.[11] In fact, guidelines suggest best supportive care in these patients except for chemosensitive tumours, such as lymphoma or some subsets of mutated non-small cell lung cancers (for example EGFR or ALK mutated), or specific cases where radiotherapy may help control symptoms,[10] but that was not the case in our patient. She would not benefit from chemotherapy or radiation because she had poor prognostic factors. Even if she had not had poor prognostic factors, chemotherapy or radiotherapy have shown limited survival benefits.[10] She survived 1 week in best supportive care and died 3 weeks and 3 days after admission which supports what is written about LC in gastric cancer. In fact, the prognosis of LC is poor as it progresses very rapidly[2] (as in our patient's case) and survival is within 2.5 to 16 weeks from the time of diagnosis.[2] However, if left undiagnosed and untreated, however, the median survival is only 4 to 6 weeks.4 In gastric cancer prognosis is even worse, with median survival of 4 weeks.[10]

This case report is intended to emphasize the importance and high index of suspicion needed to diagnose LC with SIADH as a gastric cancer presentation from unspecific symptoms because, although very rare, it is possible and there can be fatal consequences in weeks. ■

Prémios e Apresentações prévias | Awards and past presentations

Apresentado no 29° Congresso Nacional de Medicina Interna de Portugal sob a forma: e-poster com apresentação. | Presented at the 29th Portuguese National Congress of Internal Medicine as e-poster with presentation.

Declaração de Contribuição

IS - Cuidados à doente, pesquisa e elaboração do manuscrito (caso e revisão teórica) e aprovação da versão final submetida.
RS - Cuidados à doente, pesquisa de revisão teórica e aprovação da versão final submetida.
MS - Cuidados à doente, elaboração do caso clínico e aprovação da versão final submetida.
SR - Apoio diagnóstico, revisão do manuscrito e aprovação da versão final submetida.
LP - Cuidados à doente, revisão do manuscrito, aprovação da versão final submetida.
Todos os autores aprovaram a versão final a ser submetida.

Contributorship Statement

IS - Patient care, research and preparation of the manuscript (case and theoretical review) and approval of the final version submitted.
RS - Patient care, research of theoretical review and approval of final version submitted.
MS - Patient care, preparation of clinical case and approval of final version submitted.
SR - Diagnostic support, revision of the manuscript and approval of the final version submitted.
LP - Patient care, revision of the manuscript, approval of the final version submitted.
All authors approved the final draft.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Consentimento: Consentimento do doente para publicação obtido.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Patient Consent: Consent for publication was obtained.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

Correspondence / Correspondência:

Inês Silva - ines.s.silva81@gmail.com
Serviço de Medicina Interna – Área B, Unidade Local de Saúde Santa Maria, Lisboa, Portugal
Av. Prof. Egas Moniz MB, 1649-028 Lisboa

Recebido / Received: 2023/12/14
Aceite / Accepted: 2024/02/22
Publicado online / Published online: 2024/06/17

REFERENCES

1. Ino R, Sada KE, Miyauchi A, Hashimoto D, Nojima S, Yamanaka S, et al. Added Diagnostic Value of Cerebrospinal Fluid Carcinoembryonic Antigen in a Patient with Leptomeningeal Carcinomatosis as the Initial Manifestation of Gastric Cancer. Acta Med Okayama. 2021;75:659-61. doi: 10.18926/AMO/62781.
2. Boursiquot R, Krol D, Hanif S, Rojas J, Jain M. Syndrome of inappropriate

antidiuretic hormone in a patient with leptomeningeal carcinomatosis. J Med Case Rep. 2016;10. doi:10.1186/s13256-016-0862-2
3. Kim NH, Kim JH, Chin HM, Jun KH. Leptomeningeal carcinomatosis from gastric cancer: Single institute retrospective analysis of 9 cases. Ann Surg Treat Res. 2014;86:16-21. doi:10.4174/astr.2014.86.1.16
4. Guo JW, Zhang XT, Chen XS, Zhang XC, Zheng GJ, Zhang BP, et al. Leptomeningeal carcinomatosis as the initial manifestation of gastric adenocarcinoma: A case report. World J Gastroenterol. 2014;20:2120-6. doi:10.3748/wjg.v20.i8.2120
5. Thajudeen B, Salahudeen AK. Role of tolvaptan in the management of hyponatremia in patients with lung and other cancers: Current data and future perspectives. Cancer Manag Res. 2016;8:105-14. doi:10.2147/CMAR.S90169
6. Hwang K, Jeon DH, Jang HN, Bae EJ, Lee JS, Cho HS, et al. Inappropriate antidiuretic hormone syndrome presenting as ectopic antidiuretic hormone-secreting gastric adenocarcinoma: A case report. J Med Case Rep. 2014;8. doi:10.1186/1752-1947-8-185
7. Dimitriadis GK, Angelousi A, Weickert MO, Kaltsas G, Grossman A. paraneoplastic endocrine syndromes. Endocr Relat Cancer. 2017;24:173-90. doi: 10.1530/ERC-17-0036.
8. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. Oncologist. 2012;17:756-65. doi:10.1634/theoncologist.2011-0400
9. Kusumoto T, Kimura Y, Sugiyama M, Ohta M, Tsutsumi N, Sakaguchi Y, et al. Leptomeningeal carcinomatosis originating from advanced gastric cancer : a report of three cases and review of the literatures. Fukuoka Igaku Zasshi. 2013; 104:456-63. doi:10.15017/1430780
10. Cunha R, Godinho J, Inácio M, Galriça Neto I. Palliative approach to leptomeningeal carcinomatosis in oesophagogastric junction cancer. BMJ Case Rep. 2019;12. doi:10.1136/bcr-2019-230114
11. NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers Version 1.2023 [Internet]. National Comprehensive Cancer Network; 2023 [cited 2024 Feb 2]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1425