



## Wernicke encephalopathy as rare complication of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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### ABSTRACT

**BACKGROUND:** Peritoneal carcinomatosis of gastric origin is a frequent event with poor survival. A new promising approach is the association of the Cytoreductive Surgery (CRS) with the Hyperthermic Intraperitoneal Chemotherapy (HIPEC), which yet is characterized by high morbidity and mortality.

We report, to our knowledge, the first case of Wernicke Encephalopathy (WE) complicating CRS plus HIPEC. WE, caused by a deficiency of thiamine, is characterized by ataxia, ocular motor cranial neuropathies and changes in consciousness.

**METHODS:** A patient affected by gastric cancer with peritoneal seeding, submitted to CRS plus HIPEC, in 4th post-operative day had manifested the appearance of flapping tremors, with positive manoeuvre of Mingazzini, impaired vision and mental confusion. The brain Magnetic Resonance Imaging (MRI) confirmed the clinical suspicion of WE. Even though the appropriate therapy was promptly applied, the patient died in 10th post-operative day.

**CONCLUSION:** WE is an uncommon neurological disorder. Only 16% of these patients inadequately treated recover fully, with a mortality rate of 10–20%. We consider useful to report this case, because it is the first time that WE is correlated to CRS plus HIPEC.

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## 1. Introduction

Peritoneal carcinomatosis (PC) of gastric origin is a frequent event even in the early phase of the disease, but especially in advanced cases. PC, once established, is associated with poor survival as shown by many phase III trials that reported median survival ranging from 1 to 13.8 months [1] and no survivors at five years [2]. Investigators worldwide have continued to study potential treatment options for patients with gastric cancer with limited carcinomatosis, encouraged by the results, obtained in a small but meaningful number patients with carcinomatosis of appendiceal and colorectal origin [3–5] with the association of Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Despite CRS plus HIPEC are burdened by a high morbidity

[6] WE has never been recognized among complications. WE, an uncommon neurological disorder described for the first time by Carl Wernicke [7] is caused by a deficiency of thiamine and is characterized by a classical triad of symptoms, consisting of ataxia, ocular motor cranial neuropathies and changes in consciousness [8,9]. We report, to our knowledge, the first case of WE complicating CRS plus HIPEC used as treatment of peritoneal carcinomatosis of gastric origin.

## 2. Case history

A 60 year-old man was referred to our institution for a poorly differentiated adenocarcinoma of the gastric body. He was a moderate drinker (about 0.5–1 glass of wine/day) and non-smoker. His BMI was 23.5. His medical history was not characterized by nothing relevant. Preoperative oncological staging revealed the involvement of the gastric serosal and the presence of a cleavage plane with the pancreas. The patient was submitted to a D2 subtotal gastrectomy according to Roux. A lesion white-yellowish, found on the left diaphragmatic peritoneum, was removed and its intraoperative histological examination demonstrated the metastatic origin, while

**Abbreviations:** WE, Wernicke Encephalopathy; PC, peritoneal carcinomatosis; MRI, magnetic resonance imaging; HIPEC, Hyperthermic Intraperitoneal Chemotherapy; CRS, Cytoreductive Surgery; CDDP, cisplatin; ICU, Intensive Care Unit; BMI, body mass index; p.o.-day, pos-operative day.

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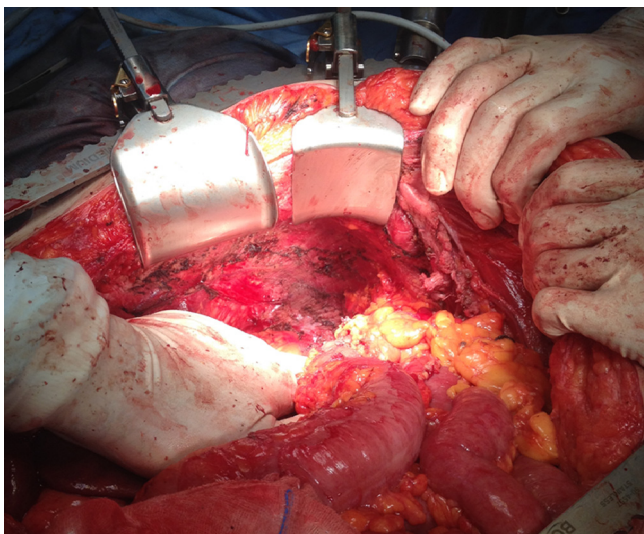


Fig. 1. Left diaphragm after peritonectomy.

the cytological exam of peritoneal lavage was negative. Therefore, the patient was submitted also to subtotal left diaphragmatic peritonectomy (Fig. 1) and HIPEC with closed abdomen technique with 191 mg of cisplatin (CDDP) plus 25 mg of Mitomycin C for 60 min. Histological examination of the stomach showed an invasive malignant proliferation, extensively ulcerated, infiltrated the gastric wall up to the tunica serosa, characterized by irregular glands with hyperchromatic nuclei and non-cohesive individual cells infiltrating the stroma. Morphological features were consistent with poorly-differentiated gastric adenocarcinoma (Fig. 2). The pathological examination of the twenty removed lymph nodes demonstrated that two perigastric nodes were metastatic. The definitive exam confirmed the neoplastic nature of the peritoneal nodule (Fig. 3). The post-operative pathological staging was therefore pT4aN1M1.

After 24 h in Intensive Care Unit (ICU), the patient was transferred in surgical department. In 4th post-operative (p.o.)-day, in absence of other complications, occurred the appearance of flapping tremors, with positive manoeuvre of Mingazzini, impaired vision and mental confusion. The patient was submitted to a brain MRI, that showed, in T2-weighted scans, a hyperintense area in the periaqueductal gray matter; after intravenous (i.v.) administration of Gadolinium was demonstrated the highlight involvement of the mammillary bodies. Therefore the imaging, also at the light

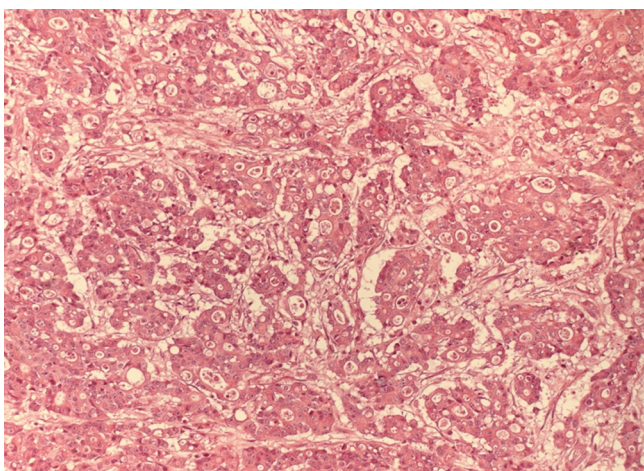


Fig. 2. Histological examination of the gastric lesion.

of clinical picture, allowed to perform the diagnosis of WE. The patient was transferred again to the ICU and was submitted to the treatment with thiamine 100 mg daily i.v. Nevertheless, in 10th p.o.-day, he died.

### 3. Discussion

In literature, CRS plus HIPEC are correlated with morbidity and mortality rates that ranges from 12 to 57% and from 0.9 to 11% [7] respectively. Comparing the various data of the major records that have calculated the incidence of grades III–IV events, the principal complications are anastomotic leaks, digestive perforations, biliary fistula, pancreatic fistula, ileus/gastric stasis, intraperitoneal abscesses, pancreatitis, nausea/vomiting, small bowel obstruction, urinary disturbance, bleeding, respiratory distress [7]. In the literature we did not find any case of WE complicating CRS plus HIPEC. WE is an uncommon neurological disorder described for the first time in 1881 by Carl Wernicke, characterized by a classical triad of symptoms consisting of ataxia, ocular motor cranial neuropathies and changes in consciousness [8]. A deficiency of thiamine is responsible for the complex symptoms characterizing this syndrome. In fact, WE occurs primarily in the alcoholics while, in the 23% of cases, it can be associated with some non-alcoholic conditions (prolonged intravenous feeding, hyperemesis gravidarum, anorexia, refeeding after starvation, thyrotoxicosis, regional enteritis, malabsorption syndromes, hemodialysis, peritoneal dialysis, uremia, HIV, malignancy, restoration stage of severe acute pancreatitis, and gastroplasty with postoperative vomiting) [8]. Animal studies showed that also tumor growth might be related to the depletion of tissutal thiamine stores, apparently because of increased thiamine utilization, and some clinical reports have underlined that secondary thiamine deficiency can be associated with chemotherapy [9]. All these conditions lead to decreased activation of thiamine pyrophosphate from thiamine, that serves as a cofactor for three critical enzymes in the intermediate carbohydrate metabolism: transketolase, ketoglutarate dehydrogenase and pyruvate dehydrogenase complex [10].

Actually a certain diagnosis is performed only in 5–14% of cases [11]. The diagnosis criteria require 2 of the following 4 signs: dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction, and either an altered mental state or mild memory impairment, even if only about 16% of patients had the classic clinical triad, and 19% had no clinical signs. The gold standard in imaging is MRI with a sensitivity of 53% and a specificity of 93% [11]. Actually only 16% of patients with WE inadequately treated recover fully, with a mor-

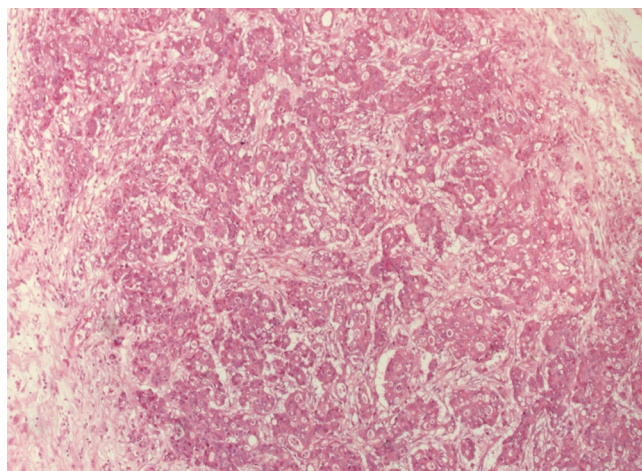
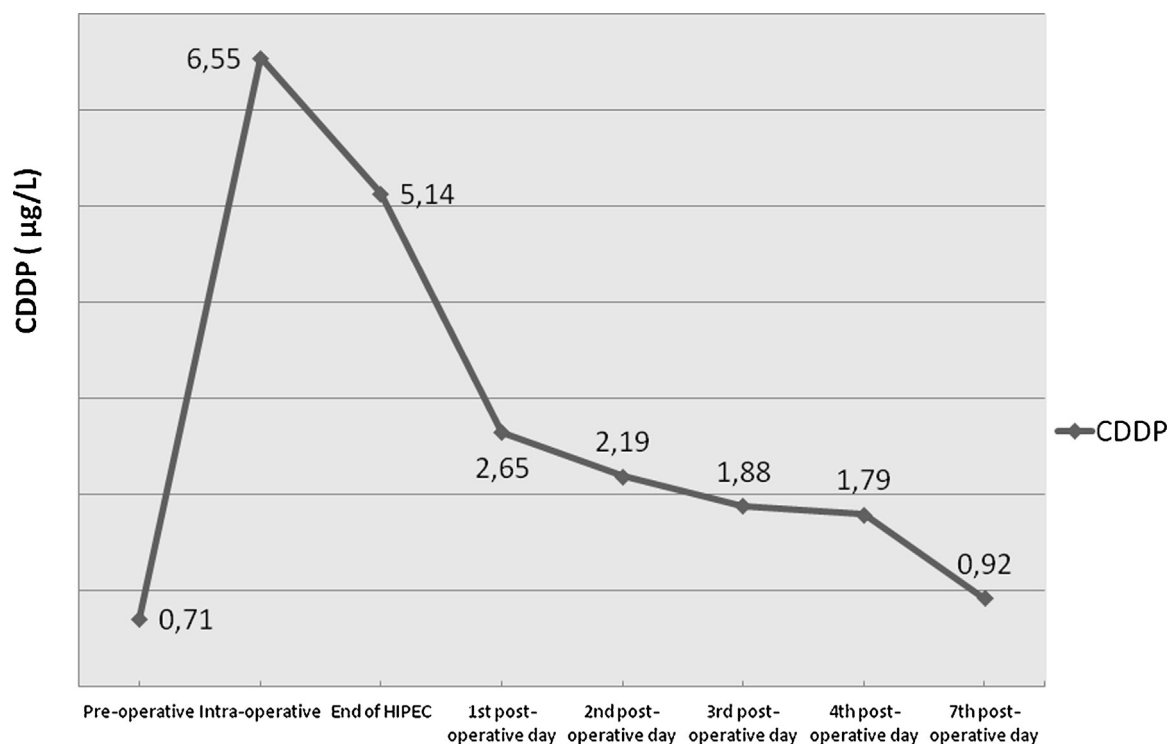


Fig. 3. Microscopic appearance of metastatic deposits in peritoneal tissue.



### Timing of CDDP serum levels

**Fig. 4.** The graph shows cisplatin (CDDP) serum level trends with error bars as standard deviation. On the right are also reported the values of standard deviation in order. In the X-axis (or abscissa axis) there is reported the time in days. The first three values are respectively at 0 time, in the middle of perfusion and at the end of perfusion.

tality rate of 10–20% [8]. The treatment consists in the immediate administration of intravenous (i.v.) thiamine. The clinical response after administering thiamine is usually striking and rapid enough to be virtually diagnostic. Hence, the prognosis of WE depends on the stage of disease and prompt institution of therapy with thiamine [10].

In our clinical case the diagnosis of WE was performed on the basis of the typical clinical triad, characterized by positive Mingazzini manoeuvre, impaired vision and mental confusion. MRI documented in T2-weighted scans, a hyperintense area in the periaqueductal gray matter and, after i.v. administration of Gadolinium, the highlight involvement of the mammillary bodies. These instrumental findings permitted to confirm the clinical diagnosis of WE, for which the patient was transferred in ICU. Notwithstanding the prompt therapies, the patient, in 10th p.o.-day, died, in accordance with the data reported in other manuscripts [12], which show that a number of patients can die even if properly treated.

As our patient was not heavy drinker, nor malnourished, we believe, as reported in literature [9], that the onset of the WE can be related to chemotherapy and to primary tumor, that, by increasing metabolism, had led to the depletion of thiamine.

The peculiarity of our case is to be identified in the intraperitoneal administration route of chemotherapy, which should reduce the systemic effects.

We have already shown [13], that the serum level of cisplatin (Fig. 4), although intraperitoneally administered, peaks ( $6.52 \pm 1.61 \mu\text{g/L}$ ) during perfusion, remains high ( $1.79 \pm 0.76 \mu\text{g/L}$ ) up to the 4th p.o.-day, and only in the 7th p.o.-day, returns to the basal values ( $0.92 \pm 0.1 \mu\text{g/L}$ ), whereby also the HIPEC may be responsible for systemic complications.

In light of this case report, we believe useful to include, among potential complications of CRS plus HIPEC, also WE.

### Consent

Authors declare that they have obtained written informed consent from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

### Conflict of interest

All authors declare that they have not any conflict of interest.

### Funding

The authors declare there are not any sponsors involvement.

### Ethical statement

The authors declare that all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Institutional and National) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from the patient for being included in the study.

### Authors contribution

Antonio Macristudy concept or design, data collection, data analysis or interpretation and reviewer, writing the paper.

Francesco Fleres contributor, corresponding author, translator.

Antonio Ieni contributor.  
 Maurizio Rossitto contributor.  
 Tommaso Mandolino contributor.  
 Salvatore Micalizzi contributor.  
 Francesco Iaropoli contributor.  
 Carmelo Mazzeo contributor.  
 Massimo Trovato contributor.  
 Eugenio Cucinotta contributor.  
 Edoardo Saladino contributor, reviewer.

#### Guarantor

Antonio Macrì.  
 Edoardo Saladino.  
 Francesco Fleres.

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