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Case report

Beware of lethal Wernicke's encephalopathy after cytoreductive surgery with HIPEC for peritoneal pseudomyxoma: Case report of morbidity and mortality review

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ABSTRACT

Background: Pseudomyxoma peritonei (PMP) arising from the appendix is a rare entity. Complete cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is the only established curative treatment, and is reputedly linked to high morbidity and mortality.
We report, to our knowledge, the first case of delayed lethal Wernicke encephalopathy (WE) complicating CRS with HIPEC for an appendicular PMP. WE, caused by a thiamine deficiency, is characterized by ataxia, nystagmus and changes in consciousness.
Methods: A patient underwent complete CRS with HIPEC for a low grade mucinous appendicular tumor at the stage of PMP with a peritoneal index of 31, and was readmitted at POD 36 for persistent vomiting and vague neurological symptoms of mental confusion. The classic triad of WE appeared tardily. Although thiamine substitution was promptly applied, the patient died at POD53.
Conclusion: WE is an uncommon and severe neurological disorder with a mortality rate up to 20 % and only 16 % of treated patients can fully recover. This diagnosis should always be anticipated in patients undergoing major surgery such as CRS- HIPEC. Efficient treatment should be quickly introduced in order to avoid a lethal outcome.

1. Introduction

Pseudomyxoma peritonei (PMP) is a rare entity characterized by free-floating mucin produced by peritoneal tumor implants. This condition most commonly originates from a ruptured appendicular mucinous neoplasm, but the ovaries or another intraperitoneal organ can also be involved. Complete cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is the only curative treatment for PMP arising from the appendix and is linked to improved outcomes in terms of survival and quality of life [1,2].

CRS-HIPEC remains a major complex procedure [3,4] and is associated with high operative mortality and morbidity especially in cases of high peritoneal cancer index (PCI) with a significant impact on patients' quality of life [5,6].

From all the complications associated with this treatment, Wernicke's encephalopathy (WE) has been reported only once in the immediate postoperative course of a CRS-HIPEC for gastric carcinoma [7].

Morbidity and mortality reviews (MMRs) are a forum to discuss adverse events associated with patient care. Following a systematic and systemic framework, MMRs represent a unique opportunity to identify deficiencies in an organization or patient care that potentially contributed to a complication or death. They have the potential to improve patient outcomes, quality of care, attitudes towards patient safety and they contribute to the education of clinical staff [8].

We have established in our department a weekly procedure of MMR to examine all cases of severe complications occurring within 90 postoperative day [9]. A root cause analysis [10] is performed based on the ALARM framework from the French High Authority of Health (HAS) [11], to analyze contributing factors and suggest measures of improvement in order to prevent or detect this lethal situation.

After this unusual complication, the case was discussed as

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recommended by our team, in a multidisciplinary MMR regrouping anesthesiologists and surgeons.

Based on this MMR, we describe to our knowledge the first case of delayed lethal WE after an appendicular PMP treated with CRS-HIPEC.

This case report and review of all the published literature, aims to report and discuss the challenges in the diagnosis and management of WE following CRS-HIPEC and suggest some actionable prevention measures not only in a low/middle income country [12].

2. Case presentation

We report this case in compliance with the SCARE 20202 guidelines [13].

A 50 years old female patient was referred to our institution for a low grade mucinous appendicular tumor at the stage of PMP with a peritoneal index of 31. She was previously treated for depression and had otherwise no previous medical or surgical history and no history of alcohol consumption nor smoking. After preoperative oncological staging and anesthesia evaluation, the patient underwent complete cytoreductive surgery (CC0) including: a total colectomy, bilateral oophorectomy, cholecystectomy, greater and lesser omentectomy, parietal and subtotal right diaphragmatic peritonectomy as well as fulguration of mesenteric nodules. The CRS was followed by administration of HIPEC following Gustave Roussy protocol (at oxaliplatin 460 mg/m^2) by open abdomen technique after systemic chemotherapy (400 mg/m^2 fluorouracil and 20 mg/m^2 folinic acid) [14]. The patient was transferred to the surgical department after 3 days in the intensive care unit (ICU). At POD4 the patient was operated for an ileal perforation with confection of a temporary ileostomy. The patient was discharged at POD19.

Four days later (POD23), the patient was readmitted to the surgical department for abdominal pain with hyperemesis and poor oral food intake. An abdominal CT-scan revealed an abdominal collection that was drained under sonographic guidance and a treatment regimen of antibiotics and anti-emetics was started. Although the control sonography confirmed the drying off of the collection, several episodes of vomiting persisted. Diagnosis of gastroplegia was retained and total parenteral nutrition (TPN) was introduced in addition to intravenous erythromycin. The vomiting regressed and the patient was discharged under antiemetics.

The patient consulted via ambulance the emergency ward at POD36 was readmitted for reappearance of vomiting with food refusal. She presented symptoms of mental confusion and apathy. A psychological evaluation suggested a relapse of her depression and she was put on IV antidepressants and anxiolytics with a 72 hour improvement before the patient developing dysarthria and agitation suggesting an organic encephalopathy. Upon examination, the patient was disorientated to people, space and time, with nystagmus and hand tremors.

A cerebral MRI under sedation was performed revealing hyperintense signals in the periaqueductal gray matter and excluded other intracranial pathology (Fig. 1). On the account of the clinical and radiology findings, diagnosis of Wernicke encephalopathy was retained.

Due to a national shortage in IV thiamine, the patient received injections of 100 mg thiamine twice a day for four days. Treatment was abruptly stopped for 2 days. During this period, the patient received oral form of a multivitamin B complex. Treatment was reinstated by 200 mg of IV thiamine twice a day, as soon as it became available but without any significant improvement of the clinical symptoms. The patient died at POD53.

This unusual complication was discussed in our weekly morbidity and mortality review (MMR). We used a root cause analysis [10] based on the ALARM framework [11] transcripted to an Ishikawa diagram, to identify the contributing factors resulting in this complication.

From the patient category, two elements were identified: the complexity of the surgery and the unknown history of mental illness which led to a delay in diagnosis. From the task category, the absence of a clear protocol of treatment and supplementation was identified as a contributing factor.

Following this MMR, the main recommendation issued was to elaborate a protocol of systematic thiamine supplementation to all patient candidates to a CRS-HIPEC procedure. This protocol is now fully implemented.

3. Discussion

We report the first case of a lethal Wernicke's encephalopathy occurring more than one month after CRS-HIPEC for an appendicular PMP. The postoperative course was marked by severe vomiting and poor dietary intake requiring TPN, resulting in the patient's death.

Morbidity and mortality reviews when conducted at a regular frequency, through a standardized procedure and case presentation with clearly defined goals [15–17] can identify system-based issues and allow for ample analysis of the root causes and possible underlying contributing factors of the adverse events [18] and thus, shifting MMR towards a quality improvement scope.

To better reflect patient safety culture, this knowledge must be translated into meaningful quality improvement initiatives through

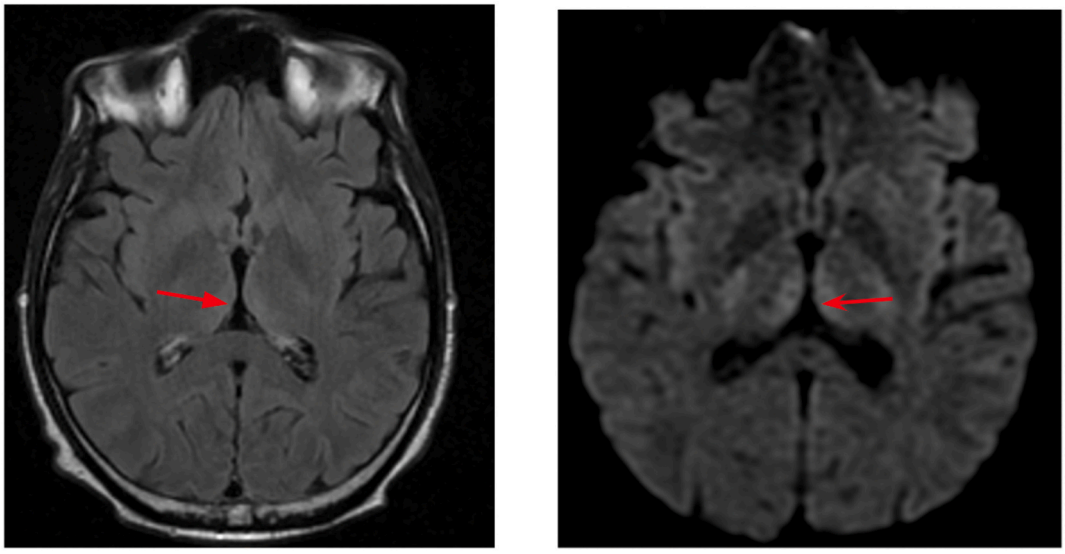

Fig. 1. Cerebral MRI images showing hyperintense signal of the periaqueductal gray matter.

specific and detailed action plans [19].

CRS-HIPEC is the established treatment not only for ovarian cancer [20] but also PMP originating from the appendix. Its positive effect on overall and disease-free survival has been proven in literature [21]. Nevertheless, this surgery is linked to a high postoperative morbidity and mortality ranging from 12 to 57 % and from 0.9 to 5.8 % [2] respectively. Postoperative complications described include mainly anastomotic leak and intra abdominal abscess, ileus, pulmonary complications, and chemotherapy induced hematological or renal failure [12]. In the literature, only one paper reported a Wernicke encephalopathy complicating CRS-HIPEC for gastric carcinoma [7].

This rare neurological disorder was first described by Carl Wernicke in 1881, and was later attributed to thiamine deficiency (TD). This water soluble vitamin acts as a cofactor for enzymes involved in energy production in muscles, hepatocytes, and neurons. It is absorbed in the duodenum and reaches the blood through passive and active mechanisms [22]. Thiamine cannot be synthesized by the human body and needs to be consumed regularly at a daily intake of approximately 1.2 mg [23]. The healthy body stores a buffer of 2–3 weeks of thiamine.

The main cause of TD is alcohol abuse creating a hypermetabolic state and thus, accelerated thiamine consumption. The same mechanism is described in growing tumors due to a rapid cell turnover [24].

Chronic dietary thiamine deficiencies include poor absorption or low intake and are found in: recurrent vomiting, celiac disease, pyloric obstruction, or gravidic hyperemesis, TPN [25]. Cases of WE after complex gastrointestinal surgery are increasingly reported, and are due to similar mechanisms [25–29]. Our patient had several plausible factors for WE: major cytoreductive surgery with HIPEC for a rapidly evolving tumor, a postoperative course marked by gastroparesis, severe vomiting and poor dietary intake requiring lengthy total parenteral nutrition.

Early manifestations of TD are often non specific, including fatigability, frequent headaches and abdominal discomfort. WE is characterized by the typical association of three symptoms: mental confusion, ataxia, and nystagmus. This triad may appear 2 to 8 months after surgery [28] but is complete in only 16 to 25 % of WE [28,30]. Consequently its use as a reliable diagnostic tool has been abandoned. Caine et al. [31] proposed operational criteria to identify WE in alcoholic patients with a sensitivity of 85 %; diagnosis can be made when patients have 2 of the following 4 signs: nutritional deficiency; ocular signs; cerebellar signs; altered mental status or mild memory impairment. In the present case we report latent onset of non-specific symptoms of Wernicke's encephalopathy, with signs of the classic triad appearing tardily.

The variety of clinical presentations and the lack of a reliable test make WE's diagnosis challenging and explains diagnosis and treatment delays. While there are laboratory tests for measurement of serum thiamine concentration, an accurate measure of the brain's concentration of thiamine in its different forms is difficult to detect [32]. The measure of seric thiamine levels were not available in our hospital reason why they were not performed in this patient.

To corroborate the diagnosis, our patient had a cerebral magnetic resonance imaging (cMRI) suggesting signs of metabolic encephalopathy. Several authors reported that cMRI can describe contrast enhancement of the periaqueductal gray matter with mamillary bodies and midbrain tectum involvement. In view of its high specificity (93 %), cMRI can confirm a clinically suspected WE while ruling out other intracranial causes. Nevertheless, cMRI is a costly exam that lacks sensitivity (53 %) to be a reliable diagnostic tool [33]. Besides, it can be difficult to realize in case of confusion or agitation.

The treatment of WE whenever suspected is the urgent administration of seric thiamine. There is no consensus on the optimal dose, form or duration of treatment. The European guidelines recommend high-dose intravenous (IV) thiamine: 200 mg IV three times a day until symptom improvement; while the UK guidelines [34] recommends IV injection of 500 mg three times a day for 3 days or longer. There is however, insufficient evidence on the superiority of one dosage over the other.

Our patient received IV thiamine however the optimal dose was not reached during the product shortage which led to a lethal issue of the patient at POD42.

WE is a severe neuropsychiatric emergency that may be lethal in 17 % of reported cases [35,7,36]. Even when TD is compensated, only a few patients will have a complete symptom resolution, most of them may keep residual cognitive deficits consisting of memory loss, confusion, spatio-temporal disorientation, cerebellar and ocular sequelae.

There are several misconceptions about WE and the evidence is insufficient to guide its diagnosis and treatment. However, mindful suspicion of WE should be always maintained in order to ensure a quick and efficient treatment [37]. To summarize, we would like to insist on the following points:

- WE can appear in non alcoholic patients. Several papers report WE particularly in cancer patients undergoing gastrointestinal surgery.
- The classic triad is not always present. Caine's criteria proved high sensitivity and specificity in alcoholic patients. Although they haven't been studied in a non-alcoholic context, these criteria provide a broad spectrum of symptoms allowing one to think of WE in patients with risk factors of TD.
- Treatment should be administered when the diagnosis is suspected, by IV injection of thiamine at 200 mg three times a day until symptoms resolve.
- Postoperative early resumption of oral intake should be encouraged. However, in case of necessary TPN, systematic supplementation with IV thiamine is mandatory.
- A prolonged administration of glucose or dextrose causes a hypermetabolic state [37] and thus must be associated with thiamine supplementation.
- More studies are mandatory to assess preoperative prevention: nutritional preparation with thiamine in selected patients, namely candidates for major gastrointestinal surgeries.

4. Conclusion

Wernicke's encephalopathy is a severe neurological disorder potentially lethal, but foreseeable. This diagnosis should always be anticipated in patients undergoing major surgery such as CRS-HIPEC. Physicians must maintain a high index of suspicion of WE and quickly introduce an efficient treatment in order to avoid a lethal outcome.

Informed consent

Informed consent was obtained from individuals included in this study. The consent for publication of data has been taken from the patient's husband.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethical approval

Not applicable. This study being retrospective, approval by the Ethics Committee of Biomedical research was not necessary according to the local reglementation (Law 28.13, article 2).

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CRediT authorship contribution statement

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Declaration of competing interest

Authors state no conflict of interest.

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