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Delayed diagnosis of Wernicke encephalopathy with irreversible neural damage after subtotal gastrectomy for gastric cancer: A case of medical liability?



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ABSTRACT

INTRODUCTION: Wernicke's encephalopathy (WE) is a neurological syndrome caused by thiamine deficiency, and clinically characterized by ophthalmoplegia, ataxia and acute confusion. In developed countries, most cases of WE have been seen in alcohol misusers. Other reported causes are gastrointestinal tract surgery, hyperemesis gravidarum, chronic malnutrition, prolonged total parenteral nutrition without thiamine supplementation, and increased nutrient requirements as in trauma or septic shock. WE is a well-known postoperative complication of gastric restrictive surgery for morbid obesity, after which patients often experience protracted nausea and vomiting, leading to malnutrition and massive weight loss.

PRESENTATION OF CASE: This case report concerns WE occurring in a patient who underwent Roux-en-Y subtotal gastrectomy for gastric cancer, and subsequently experienced neurological symptoms that proved irreversible probably due to the lengthy time elapsing between their clinical presentation and the diagnosis of WE.

DISCUSSION: There have been some reports of WE occurring after total or subtotal gastrectomy for gastric cancer in non-obese patients with no history of alcoholism, but monitoring for WE has yet to be recommended in the clinical guidelines in this setting (as it has for bariatric surgery). Because of its rarity and variable clinical presentation, WE is often under-diagnosed and under-treated, and confused with other neurological problems.

CONCLUSION: There is an urgent need for the specific guidelines to take into account not only the neoplastic follow-up of such patients, but also the possible side effects of necessary surgery, since this could help to ensure the timely diagnosis and management of WE in this setting, and to avoid, when possible, claims for medical malpractice that may cause enormous costs both in economical and professional terms.

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1. Introduction

The present work has been reported in line with the SCARE criteria [1].

Wernicke's encephalopathy (WE) is a neurological syndrome caused by thiamine deficiency, and clinically characterized by ophthalmoplegia, ataxia and acute confusion [2,3]. WE is a rare, but quite well-known disease and its prevalence is 0.4–2.8 per 100 thousand population.

In surgery for morbid obesity, thiamine deficiency has been reported in 0–29% of patients preoperatively, and in 31% at five years postoperatively [4], and WE has been widely described in patients who have undergone surgical procedures, such as gastric

bypass [5–7], sleeve gastrectomy [8], vertical banded gastroplasty [9], and gastric banding [10], making the occurrence of WE a well-known postoperative complication of gastric restrictive surgery.

A reduction in thiamine levels has been described in the literature [11] in non-obese patients with no history of alcoholism who have undergone total or subtotal gastrectomy for gastric cancer, and WE has been reported after subtotal gastrectomy in patients with malignant stomach neoplasms [12].

The case report we describe highlights several important management principles when faced with such a rare complication in neoplastic patients, and it provides evidence that thiamine therapy is still an accepted method of diagnosis of Wernicke's encephalopathy, since the risk of developing encephalopathy has not been taken into account in the case here presented.

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2. Presentation of case

A 71-year-old man with a body mass index of 22 kg/m² and a medical history of rheumatoid arthritis and type 2 diabetes developed a gastric cancer located in the antrum, which was diagnosed by biopsy. At the time of the cancer diagnosis, the patient's laboratory data showed no evidence of malnutrition, nutritional deficiencies or metabolic disease, and his liver and renal function tests were within normal range. In the absence of any associated gastric lesions, the patient underwent subtotal gastrectomy with Roux-en-Y anastomosis.

On pathological examination, the surgical specimen showed poorly-differentiated, intestinal-type adenocarcinoma, clear resection margins, and vascular and perineural invasion. The cancer was staged as IIIA (pT3 N2 G3) according to the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) Classification [13].

A week after the operation, the patient experienced isolated episodes of confabulation, which regressed after treatment with quetiapine and phenothiazine. He was discharged in good general condition.

Five days later, he was readmitted to hospital with recurrent episodes of vomiting and confusion. He showed no signs of malnutrition, such as hypoalbuminemia or steatorrhea. Laboratory tests showed electrolytes within normal range (n.r.), RBC $4.00 \times 10^{12}/L$ (n.r. $4.40\text{--}5.60 \times 10^{12}/L$), and Hgb 9.2 g/dL (n.r. 13.0–17.0 g/L). Esophagogastroduodenoscopy and barium X-ray ruled out any obstruction at the site of anastomosis. Neurological examination revealed a moderate cognitive impairment with confabulation. The psychiatrist attributed the patient's altered mental state to a maladaptive reaction to the surgical procedure. The patient was treated with paroxetine and quetiapine. His mental confusion regressed and he was discharged in good general conditions.

A month later, he relapsed with psychomotor agitation and dysphagia. Laboratory findings on admission were: RBC $3.35 \times 10^{12}/L$ (n.r. $4.40\text{--}5.60 \times 10^{12}/L$), Hgb 8.2 g/L (n.r. 13.0–17.0 g/L), albumin 2.80 g/dL (n.r. 3.50–5.20 g/dL), folates 6.4 ng/mL (n.r. 3.1–20.5 ng/mL), Vit B12 614 pg/mL (n.r. 189–883 pg/mL), Vit D 27.4 ng/mL (n.r. 30–100 ng/mL). Skull CT showed no signs of any ischemia or intracranial lesions.

On cranial MRI performed on the second day after admission, axial T1-weighted images showed low-density alterations in the vermis, periaqueductal gray matter, mammillary bodies and thalami (Fig. 1). Diffusion-weighted imaging showed high-density changes in the same areas (Fig. 2). These MRI findings prompted to the diagnosis of WE and Vitamin B1 was administered intravenously. The patient died three months later in a state of general neoplastic cachexia, having made no neurological recovery. The family had asked a specialist in legal medicine to conduct a preliminary examination of the patient's case to confirm or rule out any medical malpractice, but when his general conditions deteriorated due to the cancer's diffusion, they abandoned the idea of any lawsuit against the medical practitioners involved.

3. Discussion

One of the mechanisms responsible for the onset of Wernicke's encephalopathy after gastrointestinal surgery is vomiting, which leads to malnutrition and massive weight loss [14], poor compliance with an adequate dietary intake, ingestion of excessively limited amounts of food, poor digestion and consequent malabsorption, and a reduction in the area of gastric and duodenal mucosa useful for absorbing thiamine [15].

The non-specific clinical presentation of WE can delay its diagnosis, and any diagnostic delay can be responsible for irreversible

brain damage, which usually develops after 14 days of thiamine deficiency [16]. The early diagnosis and treatment of WE are crucial to prevent persistent brain damage. In the present case, the patient had two conditions associated with a risk of WE (a surgical procedure leading to the exclusion of a portion of the gastrointestinal tract, and episodes of recurrent vomiting lasting for a month), and one of the symptoms in the classical triad for WE (changes in mental state), but his altered mental state was misinterpreted as a maladaptive reaction to his surgery. This meant that WE was only diagnosed a month after the onset of the clinical signs of the condition.

As regards the preliminary investigation to test the hypothesis of medical malpractice, it is worth taking a look at the international guidelines: the European [17] and Japanese [18] guidelines for gastric cancer surgery do not recommend any accurate follow-up to check for vitamin deficiencies in patients who undergo total or subtotal gastrectomy for gastric cancer. The British and Irish guidelines [19] recommend general nutritional support for 10–14 days in patients identified as malnourished prior to surgery, and early individual nutritional counseling with a weekly follow-up while patients are receiving chemo- and/or radiotherapy. The National Comprehensive Cancer Network (NCCN) guidelines [20] suggest that patients who have undergone gastric resection surgery should be monitored and treated as necessary for Vitamin B12 and iron deficiency. The Italian guidelines (AIOM) [21] call for a general nutritional follow-up, focusing mainly on anemization and dumping syndrome. The guidelines of the European Federation of the Neurological Societies (EFNS) [22] for the diagnosis, treatment and prevention of WE mention more than 600 cases of WE due to conditions other than alcohol use, and most commonly caused by malignant disease, gastrointestinal disease, and vomiting due to hyperemesis gravidarum, among others. It is stated in this document that no prevalence studies have been conducted on WE among non-alcoholics, and we can only speculate on the real prevalence of the condition in situations at risk. These guidelines recommend following up thiamine status for at least 6 months and parenteral thiamine supplementation in patients undergoing bariatric surgery.

There are therefore still no strong recommendations in the Italian or international literature for the strict monitoring of thiamine levels in patients undergoing surgery for gastric cancer. The relevant guidelines focus on a follow-up to check for any recurrence of the neoplasm (which poses the main problem in such cases). Conversely, accurate monitoring for thiamine deficiency is strongly recommended in the guidelines for patients undergoing bariatric surgery for morbid obesity, in whom nutrient deficiencies are the most important potential long-term complication [23].

The differential diagnosis between WE and other psychiatric and/or neurological disorders is fundamentally important because the longer appropriate therapy is delayed the greater the risk of permanent neurological damage and death. An erroneous diagnosis (as in the present case) may be due to a relatively non-specific clinical presentation or to physicians failing to recognize WE because of its rarity in clinical practice. While the lack of specific guidelines may justify the medical practitioner who does not take the possibility of WE into account, recent studies indicate that clinicians should suspect this disorder in the event of unexplained confusion or coma in malnourished and/or surgical patients.

This brings us to the question of whether a missed or late diagnosis of WE might represent a case of medical malpractice, even in the absence of specific guidelines on the matter. In our opinion, adherence to the guidelines does not necessarily mean that a clinical practitioner's conduct has been faultless. Nor should failure to adhere to the guidelines be considered alone when assessing a physician's liability and compliance with the standards of care in medico-legal investigations. Every clinical case has its own story.

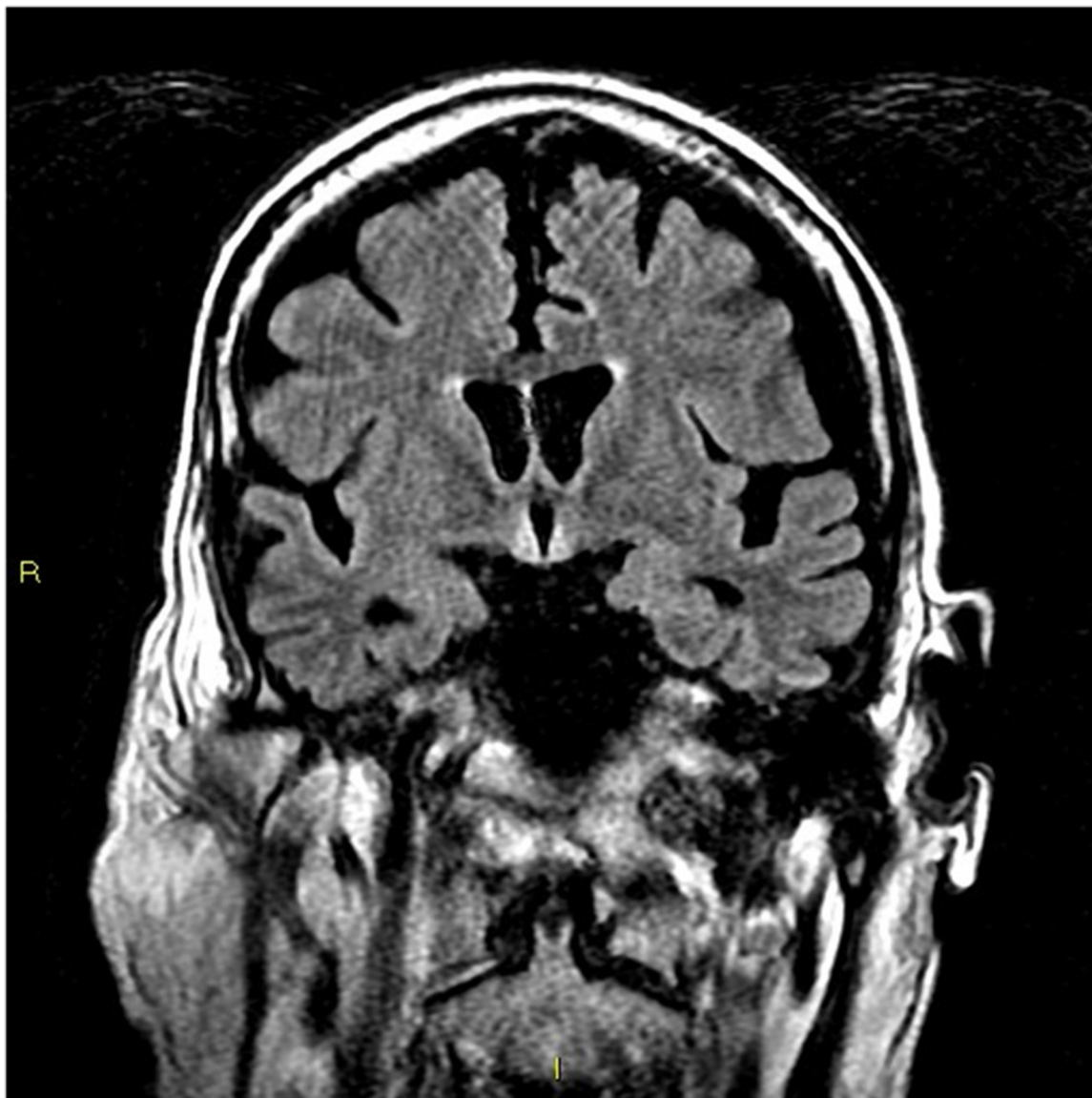


Fig 1. cranial MRI of our patient. Axial T1-weighted images show low-density alterations in the vermis, periaqueductal gray matter, mammillary bodies and thalami.

In the case reported here, the patient's non-specific clinical parameters and the absence of any detailed recommendations on the prevention of thiamine deficiency in patients treated for gastric cancer are, to our mind, the key reasons for ruling out any medical malpractice.

4. Conclusion

The early recognition or suspicion of thiamine deficiency occurring in patients who have undergone surgery for gastric cancer may be crucially important because patients with WE may become comatose and die without a prompt diagnosis of the disorder and consequent administration of thiamine.

Given the infrequent occurrence of thiamine deficiencies (although the number of case reports on this topic is increasing), the related symptoms may be misdiagnosed, and any delay in their treatment can have potentially irreversible effects on the central nervous system. It is important to bear the risk of WE in mind when dealing with surgically-treated gastric cancer patients showing acute neurological symptoms such as ataxia, nystagmus or

disorientation, and thiamine replacement should be implemented without delay whenever WE is suspected.

Early diagnosis and proper management of such rare complication are important to avoid mortality; however, other aetiologies of WE should be carefully considered and excluded, in order to avoid, when possible, claims for medical malpractice that may cause enormous costs both in economical and professional terms. There has been an error in the patient's treatment in this case, and this could have led to claims for medical malpractice.

There is an urgent need for the specific guidelines to take into account not only the neoplastic follow-up of such patients, but also the possible side effects of necessary surgery, since this could help to ensure the timely diagnosis and management of WE in this setting.

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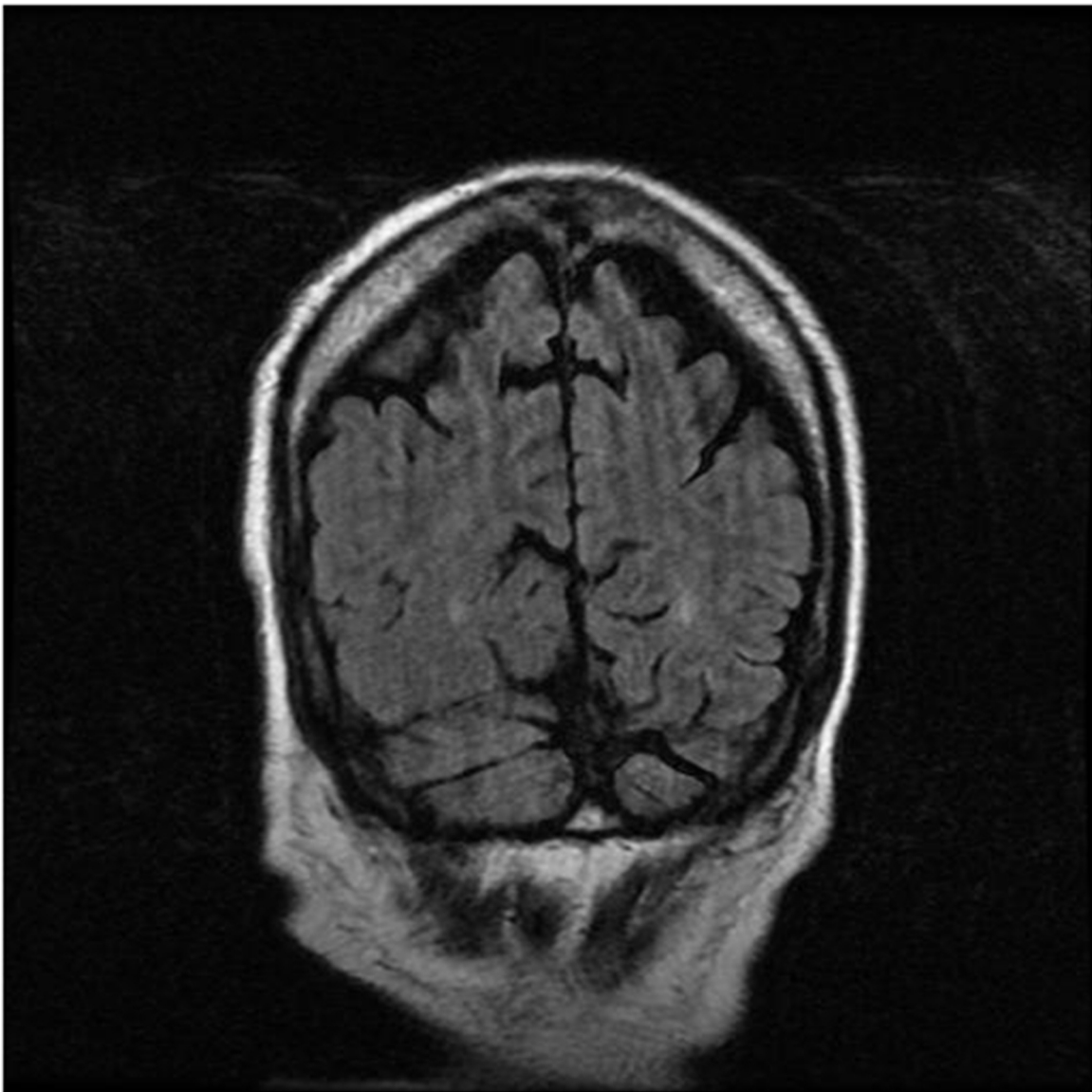


Fig. 2. cranial MRI of our patient. Diffusion-weighted imaging shows high-density alterations in the same areas.

Ethical approval

This manuscript does not refer to research involving patients, so it does not need ethical approval.

Conflict of interest

Authors have no conflicts of interest to declare.

Consent

Written informed consent was obtained from the relatives of the patient (he is dead) 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.

Authors contributions

DR identified the subject and selected the case report; PT and MB conducted the literature review and wrote the first draft of the

manuscript, LC rewrote the article and approved the subject. All Authors approved the final version of the manuscript.

Guarantor

Dr. Matteo Bolcato.

Authors have checked the spelling, grammar and syntax of the entire manuscript and they ensure the language is concise.

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