

Rhabdomyolysis after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: A Case Report

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Key Words

Gastric cancer · Peritoneal carcinomatosis · Cytoreductive surgery · Hyperthermic intraperitoneal perioperative chemotherapy · Rhabdomyolysis · Compartment syndrome

Abstract

Gastric cancer with peritoneal carcinomatosis is a disease with a poor prognosis. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal perioperative chemotherapy (HIPEC) can improve prognosis, although in most cases this should still be considered as a palliative treatment. Therefore, morbidity has to be avoided at all cost as quality of life is of utmost importance. We describe the case of a 64-year-old female with an adenocarcinoma of the stomach that was initially treated with a Billroth II gastrectomy, adjuvant chemotherapy and radiotherapy. During follow-up, the diagnosis of peritoneal carcinomatosis was made, and the patient was referred for CRS and HIPEC. Postoperatively, she developed rhabdomyolysis in both gastrocnemius muscles. Renal function remained within normal limits, but ultrasonography of the lower legs suggested the presence of bilateral abscesses. Drainage with pigtail catheters was necessary for more than 1 month, significantly impairing quality of life. The objective of this case report is to heighten awareness for this complication. Rhabdomyolysis is a rare complication of CRS and HIPEC, with a significant impact on quality of life. Prevention is necessary and can be achieved by adequate surgical positioning, using the altered lithotomy position, sufficient padding and by preventing hypovolemia.

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Background

Gastric cancer with peritoneal carcinomatosis (PC) has a poor prognosis. Median survival with systemic treatment is reported to be less than 3 months [1]. In the past, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal perioperative chemotherapy (HIPEC) improved prognosis of patients with isolated PC from other primary tumors [2–5]. In locally advanced gastric cancer with serosal or lymph node invasion, but without established PC, CRS + HIPEC was also associated with a better outcome according to three randomized controlled trials [6–8]. The same concept was then applied to gastric cancer with established PC. Several studies suggested that CRS and HIPEC could improve survival of these patients, with an acceptable morbidity and mortality [9, 10]. Patient selection is of utmost importance [11, 12]. Preoperative imaging and intraoperative staging systems estimating the extent of PC correlate with morbidity and mortality [13, 14]. Completeness of cytoreduction (CCR) and the experience of the surgical team also influence the outcome significantly, improving survival and lowering the risk of complications [15].

Complications relate to both surgery and chemotherapy [16]. We report on a rare but important complication namely rhabdomyolysis. The reported incidence of rhabdomyolysis after surgery varies widely between 0.67% in laparoscopic nephrectomy and 37–77% in gastric bypass [17, 18]. The use of different diagnostic criteria is responsible for the wide variation between these data. In the first article, rhabdomyolysis was only diagnosed after patients' complaints, whereas in the second article, creatinine kinase (CK) values were measured in all patients and rhabdomyolysis was defined as an increase of more than 5 times the upper limit. Nevertheless, body mass index is recognized as a significant risk factor [18]. Prolonged surgery and certain surgical positions are also identified risk factors for rhabdomyolysis [19]. The aim of this report is to heighten awareness for this complication.

Case Description

Presentation

A 64-year-old female presented with an invasive adenocarcinoma of the stomach. She was treated with a Billroth II gastrectomy, followed by radiotherapy and chemotherapy. Pathology reported invasion of both lymphatic and blood vessels (T3N2M0). Adjuvant treatment was well tolerated. Six months later, the patient started complaining about diffuse abdominal pain. Initially, no focus was identified. Biochemistry remained within normal limits. Another 4 months later, a follow-up CT suggested peritoneal recurrence of the gastric carcinoma. PC was described caudal from the right hepatic lobe and anterior of the distal one-third of the sigmoid. Enlarged lymph nodes were demonstrated para-aortic. Chest X-ray was normal. A PET-CT was not executed because of the low sensitivity and specificity in gastric cancer, especially after gastrectomy [20].

Treatment

The patient was referred for CRS and HIPEC after multidisciplinary consultation. She was placed in the modified lithotomy position and had intermittent compression stockings on both legs to improve venous return. Induction of anesthesia included the administration of propofol, fentanyl and rocuronium bromide intravenously. Anesthesia was maintained with target-controlled infusion of propofol. The peritoneal carcinomatosis index (PCI) according to Sugarbaker added up to a total score of 12 [21, 22]. A complete cytoreduction (CCR 0.1) was achieved. Then, HIPEC was administered by the open technique. The

peritoneum was perfused with icodextrin 1.5% until a uniform intraperitoneal temperature of 41.5°C was managed. Subsequently, 78 mg of cisplatin (50 mg/m²) and 23.4 mg of doxorubicin (15 mg/m²) were administered in three doses over a total of 90 min. During the operation, the patient stayed hemodynamically stable with a total blood loss of 900 ml. Fluid loss was compensated by 4,500 ml of crystalloid, 2,000 ml of colloid and 350 ml of whole blood transfusion. Diuresis remained above 1 ml/kg/h all the time. The total operating time was 10 h and the anesthetic time was 10 h and 50 min. The patient was transferred to the intensive care unit in a stable condition.

Postoperative Course

During the first 24 h postoperatively, the patient had a urine output of 1,500 ml. Biochemistry revealed an elevated serum CK of 2,175 U/l (normal range: 26–140 U/l) on day 0, which is not unusual after CRS and HIPEC. However, on postoperative day 1, CK levels further increased to a maximum of 9,079 U/l and urine testing revealed a myoglobinuria. The diagnosis of rhabdomyolysis was made. After removal of the peridural catheter on day 2, the patient started to complain of severe pain in both calves and paresthesias in her feet. Clinical examination of the lower legs demonstrated normal plantar and dorsiflexion, and normal arterial pulsations, excluding a compartment syndrome. Venous duplex ultrasonography excluded deep venous thrombosis but demonstrated hyperechoic areas within the muscles (fig. 1). Monitoring of the CK levels showed a gradual decline to 190 U/l on day 9. Renal function stayed within normal limits the whole time. Later on, the patient developed bilateral sterile abscesses in the gastrocnemius muscles as a complication of the rhabdomyolysis. The abscesses were punctured and drained with a pigtail catheter under the guidance of ultrasonography (fig. 2, fig. 3). Eventually the drains were removed, and the patient could be discharged after 1 month and 10 days. She was readmitted after 3 days with the same complaints, and a new ultrasonography-guided puncture was performed. Analgesics were administered if necessary, and after 8 more days in the hospital, the patient went home with the drains in situ. After 2 weeks, the catheters were permanently removed at the outpatient clinic.

Discussion

Gastric cancer with PC is a disease with a poor prognosis [1]. CRS and HIPEC can improve prognosis with acceptable mortality, morbidity and quality of life [9, 10, 23, 24]. In 2009, Glehen et al. [3] reported a multicenter cohort study of 1,290 patients with PC. CRS combined with HIPEC could achieve long-term survival in selected patients. However, they reported differences in outcome according to the primary tumor that caused PC. Gastric cancer had the poorest prognosis. In a subanalysis, Glehen et al. [9] investigated specifically those patients with PC from gastric cancer. They demonstrated a median survival of 9.2 months, which increased to 15 months in patients with CCR 0.1. In a phase III randomized clinical trial of patients with PC from gastric cancer, Yang et al. [10] reported medium survivals of 11.0 months in the CRS and HIPEC group, opposite to 6.5 months for CRS alone. In 2011, Gill et al. [24] reviewed all previous studies of CRS and HIPEC as a treatment for PC from gastric cancer. A total of ten studies were included, and analysis demonstrated a median survival of 7.9 months. Survival increased to 15 months for patients with CCR 0.1. Thus, it is possible to obtain a significant increase of survival. Patient selection is essential as CCR after CRS and HIPEC is the most important prognostic factor regardless of the origin of PC [11–13].

However, at present, CRS combined with HIPEC should be considered as a palliative treatment in most patients with PC from gastric cancer. Next to survival, morbidity and quality of life become equally important in this setting. Morbidity is graded according to the National Common Terminology Criteria for Adverse Events (NCTCAE®) [25]. In a review of morbidity after CRS and HIPEC, Glockzin et al. [16] state that the incidence of major morbidity (grades III and IV) is relatively high, but comparable to the incidence of morbidity in any other major surgery. Several independent factors, such as CCR, PCI and experience of the surgical team, are correlated with morbidity and mortality. CCR 0.1 not only improves survival, but is also associated with a lower morbidity [9–11]. Low PCI scores increase the feasibility of CCR 0.1, with possibly less extensive surgery [14, 26]. The experience of the surgical team influences the risk of morbidity, as there is a long learning curve for CRS and HIPEC [27]. Postoperative morbidity lowers quality of life. When patients recover from CRS + HIPEC, quality of life will also restore, and after 3–4 months, most patients return to baseline or better functioning [28, 29]. However, postoperative complications can significantly decrease quality of life, and this must be avoided at all times.

Most complications are surgery-related and/or a consequence of chemotherapy. In this case, we present a rare complication namely rhabdomyolysis of the lower legs. Rhabdomyolysis is defined as necrosis of skeletal muscle fibers with release of the fiber contents into the blood and urine [30]. There are many different etiologies for this condition: traumatic crush injury, hereditary muscle enzyme defects, several drugs and toxins, as well as metabolic endocrine disorders [31]. Another important etiology is prolonged immobilization, as in surgery. Persistent muscle hypoxemia due to unrelieved pressure on gravity-dependent body parts leads to a depletion of adenosine triphosphate (ATP) in the myocytes. Malfunction of a series of pumps and channels that regulate intracellular calcium levels, leads to an unregulated increase in intracellular calcium. This results in the activation of calcium-dependent neutral proteases, followed by destruction of myofibrillar, cytoskeletal and membrane proteins, ending in the disintegration of the myocytes [32]. The necrosis of muscle cells and loss of capillary wall integrity then results in transudation and exudation, ending in massive edema within the muscle compartment [33]. The edema increases the pressure within the compartment, affecting the vascular supply and forming a vicious cycle [21, 34, 35]. Further, when surgical procedures are terminated, ischemia-reperfusion injury and the following localized tissue edema can result in a continued low perfusion state in the local tissue bed [30, 33]. Additionally, a systemic hypovolemia is produced through the loss of intravascular fluid in local tissue beds further compromising perfusion. Finally, because of reperfusion, large quantities of myoglobin, potassium, phosphate, CK, lactate dehydrogenase and urate leak into the circulation, potentially leading to acute renal failure, cardiotoxicity or other complications [19, 33, 35]. This condition must not be confused with compartment syndrome. In compartment syndrome, high pressures within a muscle compartment compromise vascular supply [36, 37]. This leads to loss of peripheral arterial pulsations and neurological symptoms like paresthesias, muscular weakness or paralysis. A compartment syndrome can lead to rhabdomyolysis, and vice versa [19, 38]. However, compartment syndrome and rhabdomyolysis also exist separately. Further investigation is necessary to identify the factors that determine the exact relationship between rhabdomyolysis and compartment syndrome.

Rhabdomyolysis has been described as a complication of renal, neurosurgical and bariatric surgery [17, 18, 38–42]. Several risk factors are reported: obesity, prolonged duration of surgery, surgical positioning, hypovolemia, diabetes and hypertension. Firstly, morbid obesity is a major risk factor, as a body mass index of more than 30% of the ideal already increases the risk of developing rhabdomyolysis [41]. The extra weight puts substantial

pressure on the muscle mass [42]. Other mechanisms related to the metabolic derangement could also be involved [18, 42]. Secondly, prolonged duration of surgery is correlated with a higher incidence of rhabdomyolysis. In 1986, a study of Harris et al. [43] demonstrated that skeletal muscle tolerates ischemia for 2 h. Thereafter, ultrastructural ischemic changes occur. After 4–6 h, these changes become irreversible [44]. Thirdly, surgical positioning is also important. Various case reports in multiple disciplines describe rhabdomyolysis after prolonged surgery in different positions [17–19, 38, 41, 45]. They all indicate a correlation between surgical position, surgical length and the risk of rhabdomyolysis. Accordingly, prolonged pressure on particular muscle groups leads to rhabdomyolysis. Finally, diabetes and hypertension may increase the risk of rhabdomyolysis by leading to chronic microcirculation abnormalities [18, 38]. This leads to a higher susceptibility to perfusion problems and is a predisposing factor for rhabdomyolysis.

The outcome of rhabdomyolysis is correlated to an early diagnosis [46, 47]. A high level of awareness is crucial. Treatment is focused on preserving renal function. Because of the tendency to develop hypovolemia, aggressive fluid replacement is essential [33, 39]. Urine output should be monitored by placing a urinary catheter. Then, intravenous fluids are administered by a rate of 500–1,000 ml/h to ensure a urine output greater than 150–300 ml/h [47, 48]. However, if oliguria persists, fluid overload should also be avoided. The exact composition of the fluid regimen is still under discussion. In animal studies, urinary alkalization by using sodium bicarbonate has positive effects [49]. Empirically, the administration of mannitol is also defensible as it induces osmotic diuresis as well as renal vasodilatation and is involved in free radical scavenging, although there is a risk of acidifying the urine [50]. However, clinical superiority has not been shown for these therapies when compared to the administration of normal saline solution [51]. Another point of importance is the prevention or treatment of electrolyte disorders. Particularly the control of hyperkalemia is important to prevent cardiotoxicity. Potassium can be removed from the body by kaliuresis (loop diuretics) and intestinal potassium binders [33]. In rare cases, when the kidneys no longer respond to these supportive measures, temporary dialysis can be necessary. If a compartment syndrome is present, a decompressive fasciotomy is necessary [48].

As discussed above, CRS and HIPEC is in most cases a palliative treatment for PC from gastric cancer. Therefore, prevention of complications is important. Not only because they decrease the prognosis, but also because they lower the quality of life in patients with a shortened life expectancy. There are several hypothetical methods to prevent rhabdomyolysis in this specific setting. However, morbid obesity, diabetes and hypertension cannot be changed rapidly. Hypovolemia and surgical positioning are the only two modifiable risk factors. Hypovolemia can simply be prevented by monitoring fluid loss during the operation and replacing this loss sufficiently. To reduce the risk of rhabdomyolysis by surgical positioning, various methods are proposed. Firstly, generous padding of all pressure points effectively lowers the risk of rhabdomyolysis, if properly executed [40, 45, 52]. Secondly, the modified lithotomy position increases the risk of rhabdomyolysis and compartment syndrome of the lower legs. Therefore, this position should not be used if possible. Nevertheless, if necessary, an altered lithotomy position is proposed, with support at the feet instead of the knees or lower legs by the use of St. Mark's leg holders, thereby effectively lowering the compartment pressure [37]. Another benefit of this altered position is the impossibility of compressing the lower popliteal veins. Finally, although intermittent pneumatic stockings lower pressure in the muscle compartment, in prolonged surgery one should consider not to use them during the whole operating time [53], as they eventually become a source of friction and pressure themselves.

Conclusion

This report presents a case of rhabdomyolysis after treatment for PC from gastric cancer with CRS and HIPEC. In most cases, this is a palliative treatment, thus it is essential that quality of life is secured. Therefore, all morbidity should be prevented. Rhabdomyolysis is a rare complication of CRS and HIPEC, but it can significantly decrease quality of life. Prevention is necessary and can be achieved by adequate surgical positioning, using the altered lithotomy position, sufficient padding and by preventing hypovolemia.

Disclosure Statement

The authors declare that they have no competing interests.

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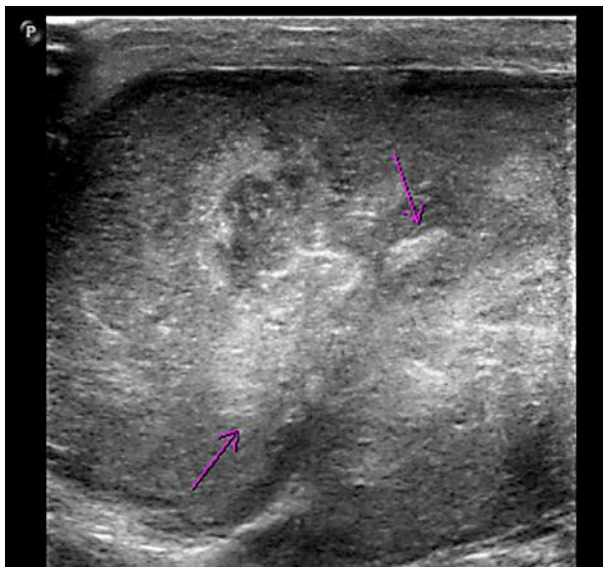


Fig. 1. Ultrasound image of the proximal gastrocnemius muscles in the axial plane: collection with hyper- and hypoechoic areas (arrows), suggesting abscess formation.

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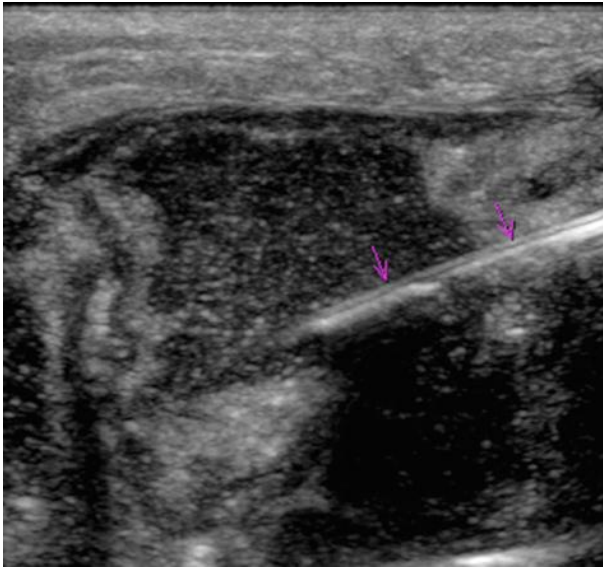


Fig. 2. Ultrasound image of an 18-gauge Chiba® puncture needle within the proximal gastrocnemius muscles in the axial plane. Ultrasonography-guided puncture of the abscess was followed by insertion of an 8F-pigtail catheter to drain the collection. This procedure was performed in both legs.



Fig. 3. 8F-pigtail catheters draining the sterile abscesses in the proximal gastrocnemius muscles.