Annals of Medicine and Surgery 27 (2018) 26–31

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Case report

A case report of acute pulmonary hypertension after hyperthermic intraperitoneal chemotherapy (HIPEC) and review of the literature

Thomas S. Zajonz[a], Michael Sander[a], Winfried Padberg[b], Andreas Hecker[b], Ruediger Hörbelt[b], Christian Koch[a], Emmanuel Schneck[a,*]

[a] Department of Anesthesiology, Operative Intensive Care Medicine and Pain Therapy, University Hospital of Giessen and Marburg, Rudolf-Buchheim-Strasse 7, 35392 Giessen, Germany
[b] Department of General and Thoracic Surgery, University Hospital of Giessen and Marburg, Rudolf-Buchheim-Strasse 7, 35392 Giessen, Germany

ARTICLE INFO

Keywords:
Case report
Respiratory failure
Right ventricular failure
Cytoreductive surgery
Oxaliplatin
5-FU

ABSTRACT

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) poses a widely used and accepted treatment option for patients with peritoneal carcinomatosis of gastrointestinal tumors. In contrast to the well-described risks and complications of intravenous cytostatic drugs, literature offers only scarce information of serious complications following HIPEC. To our knowledge no other description of rapid progressive pulmonary hypertension (PH) and consecutive respiratory failure following HIPEC have been described in current literature.
Case presentation: A 48-year-old female suffering from a recurrent appendix-carcinoma developed progressive dyspnea and fatigue six weeks after multivisceral abdominal resection and HIPEC. Medical examinations included laboratory-checks, non-invasive imaging, scintigraphy as well as invasive examinations (left-/right-heart-catheterization) and confirmed PH of unknown origin to be the cause of dyspnea. The patient died nine days after admission of respiratory failure and rapid deterioration as a result of aggravating PH.
Conclusion: Rapid progressive respiratory insufficiency due to PH following HIPEC procedure might represent a rare complication, but must be considered because of the high clinical impact. Further studies are necessary to investigate the correlation between HIPEC and PH.

1. Background

Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) represent a widely accepted therapeutic approach in oncological surgery. Severe side effects are known, but to our knowledge no other case of lethal rapid progressive pulmonary hypertension (PH) and respiratory failure following HIPEC procedure is described. We screened medical databases for known side effects of oxaliplatin, 5-Fluorouracil (5-FU), CRS and HIPEC and searched for possible reasons of PH following the HIPEC procedure.

2. Case report

This case report was written in line with the SCARE criteria [1]. Written informed consent for publishing these data was obtained from the patient.

We present the case of a 48-year old female suffering from a metastasized carcinoid of the appendix, initially diagnosed in 2010. After primary surgery in 2010 (appendectomy and follow-up resection), the patient underwent additional surgical interventions five years later caused by a local relapse (adhesiolysis, hysterectomy, bilateral adnexectomy, peritonectomy), followed by adjuvant intravenous chemotherapy with Oxaliplatin and 5-FU. In 2016, a third major surgical intervention was performed including complete parietal and partial mesenterial peritonectomy, partial resection of the small intestine, subtotal colectomy with terminal ascendostomy (“Hartmann's procedure”), cholecystectomy and omentectomy. This surgical intervention was combined with a HIPEC therapy, initiated with preoperative intravenous injection of 5-FU (400 $mg*m^{-2}$) and Calciumfolinat (20 $mg*m^{-2}$) followed by an intraabdominal HIPEC with Oxaliplatin (300 $mg*m^{-2}$). All procedures were performed by experienced senior physicians, anesthesiologists and surgeons in an university hospital setting. The patient recovered without surgical complications from that major procedure and was discharged in good clinical condition for further ambulatory treatment.

Six weeks after HIPEC procedure she developed dyspnea and progressive fatigue leading to hospital admission via ambulance in significantly reduced general condition. The next day, she evolved a sinus-

* Corresponding author.
E-mail address: emmanuel.schneck@chiru.med.uni-giessen.de (E. Schneck).

https://doi.org/10.1016/j.amsu.2018.01.007
Received 23 September 2017; Received in revised form 15 December 2017; Accepted 17 January 2018

Table 1
Overview of laboratory findings during the patient's hospital stay. Abbreviations: BNP: brain natriuretic peptide; CK: creatine kinase; CK-MB: creatine kinase myoglobin; CRP: C-reactive protein; HB: hemoglobin; PAD: post-admission day; PCT: procalcitonin.

Value	Unit (standard values)	Admission day	PAD 2	PAD 3	PAD 5	PAD 6	PAD 7	PAD 8	PAD 10
CK	12–140 (U/l)	214	145	142	145	149	160	189	177
CK-MB	0–12 (U/l)	313	260	276	296				
Troponin I	0–0.05 (µg/L)	1.88	0.62	0.26	0.08				
BNP	0–57 (pg/mL)			347	499			512	
Myoglobin	0–120 (µg/L)		47	26	27		35		
D-Dimer	0–0.49 (µg/mL FEU)	16.46	17.45	18.99	19.27				
CRP	0–1.0 (mg/L)	24.22	32.83	38.48	54.25	147.39	122.48	106.64	157.37
PCT	0–0.5 (µg/L)	< 0.5				0.7	1.1	1.2	
Leucocytes	3.9–10.2 (giga/L)	14	8.8	8.0	12.4	11.3	11.4	14.4	25.6
Hb	12.0–15.4 (g/L)	13.4	11.9	11.1	12.1	11.4	11.4	12	11.2

tachycardia (up to 150 bpm) with a preserved blood pressure and an increasing oxygen demand accompanied by rapid deterioration of the patient's clinical status. In view of the severe progress, the patient was admitted to the anesthesiological intermediate care unit for further diagnostics and therapy. Firstly, severe infection was suspected, but could be excluded by laboratory and radiologic findings. Secondly, transthoracic echocardiography was performed in order to assess the patient's hemodynamic status. It revealed neither signs of left ventricular dilatation nor hypertrophy and a good global systolic function (left ventricular ejection fraction 65%) without regional motion abnormalities. The mitral and aortic valve as well as the left atrial and ventricular diameter seemed unsuspicious. In contrast, the right heart showed under tachycardia (120 bpm) a slightly dilated ventricle and a nearly preserved right ventricular pump function (tricuspid annular plane systolic excursion (TAPSE) 18 mm). Right ventricular pressure was moderately elevated, quantified through a minor tricuspid insufficiency (systolic pulmonary artery pressure (PAP_{sys}) 35 mmHg + central venous pressure (CVP), estimated 8 mmHg [2]). Laboratory results revealed elevated cardiac enzymes and highly pathologic D-Dimers (Table 1).

Based on the clinical examination and diagnostic findings, pulmonary artery embolism has been suspected and therefore a contrast-enhanced thoracic computer tomography (CT) performed. Consistent to the echocardiographic findings the right heart was enlarged but surprisingly neither subsegmental nor central pulmonary artery embolism could be detected. Both sides of the lungs showed concomitant atypical interstitial and partially alveolar edema, consistent with an interstitial pneumonitis (Figs. 1b and 2a). Ventilation-/perfusion-scintigraphy was performed in order to exclude also peripheral pulmonary artery embolism. Some areas of combined reduced ventilation/perfusion were compatible with the mentioned alveolar consolidations in the CT, but no signs of arterial embolism could be detected. Because of the growing suspicion of significant PH as possible reason for the persistent symptoms, a left-/right heart catheterization was performed. While the coronary arteries and the left ventricular function remained unsuspicious, the right heart catheterization showed increased pressure-/resistance proportions (mean pulmonary artery pressure 34 mmHg, pulmonary vascular resistance 530 dyn*sec*cm^{-5}), narrowed cardiac output ((CO) 1.9 L*min^{-1}*m^{-2}) and minor pulmonary venous congestion (pulmonary capillary wedge pressure 13 mmHg). Regarding the positive proof of PH, oral therapy with Sildenafil was initiated. However, over the following five days initial PAP_{sys} increased from 35 mmHg up to 55 mmHg (+CVP, estimated 5 mmHg, moderate tricuspid valve insufficiency), accompanied by moderately enlarged right-sided cavities (right atrium 14 cm [2], right $ventricle_{basal}$ 37 mm). While the right ventricular function kept preserved (TAPSE 19 mm, S′ 17 cm*sec^{-1}, Tei index 0.53), moderate paradoxic movement of the septum with D-sign of the right ventricle increased. Furthermore the right ventricular outflow tract flow-profile appeared severely impaired (AT 52 ms, AT/ET 0.22), whereas inferior vena cava and liver veins were not extended. Simultaneously, blood gas analysis showed under noninvasive oxygen insufflation a progressive decrease of respiratory parameters (under 3 l O_2/min: admission: pO_2: 85.4 mmHg, 36 hours later: pO_2: 69.9 mmHg). Facing the aggravating precapillary PH and persistent reduced right ventricular function (CO 1.9 l/min/m^2) Sildenafil administration was switched from oral to continuous intravenous application. Unfortunately, the patient's respiratory situation did not improve under the PDE-5-inhibitor therapy and was aggravated by the patient's refusal to tolerate non-invasive ventilation. Considering the patient's debilitated general condition, her hopeless prognosis (multiple metastasis of bones, retroperitoneal/iliacal/inguinal lymphatic nodes, liver as well as peritoneal carcinomatosis) and most important her wish for palliative care, we stood back from further escalation of therapy. The patient died nine days after admission of global respiratory and right ventricular failure (Clavien-Dindo Classification Grade V [3]). The relatives did not acquiesce an autopsy to clarify the underlying cause of the PH. Considering the rapid progress and radiologic findings, interstitial pneumonitis led possibly to sequential development of PH.

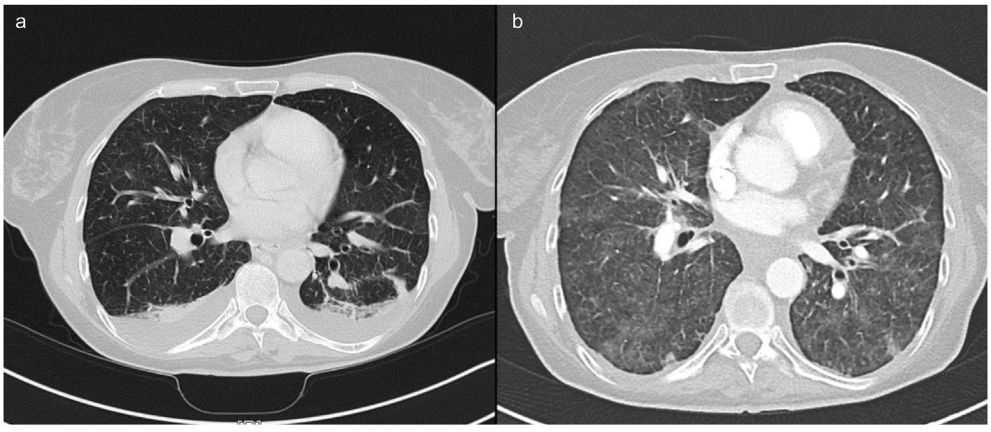

Fig. 1. Axial planes of thoracic contrast enhanced computed tomography eight days (a) and six weeks (b) after CRS and HIPEC. Eight days after surgery both lungs are inconspicuous except for minor dystelectatic pneumonia of both lower lobes and adjacent small pleural effusions. The heart shows regular dimensions. Six weeks after CRS and HIPEC the data display extensive atypical interstitial and partly alveolar edema. No signs of pulmonary artery embolism can be detected (not visible in demonstrated plane).