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Case report

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

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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-

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**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.

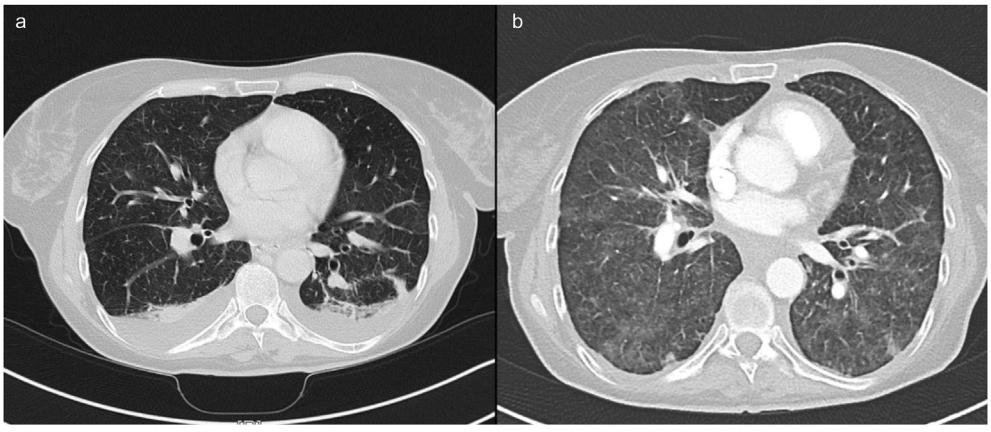


**Fig. 1.** Axial planes of thoracic contrast enhanced computed tomography eight days (a) and six weeks (b) after CRS and HIPEC. Eight days after surgery both lungs are inconspicuous except for minor dystelectatic pneumonia of both lower lobes and adjacent small pleural effusions. The heart shows regular 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).

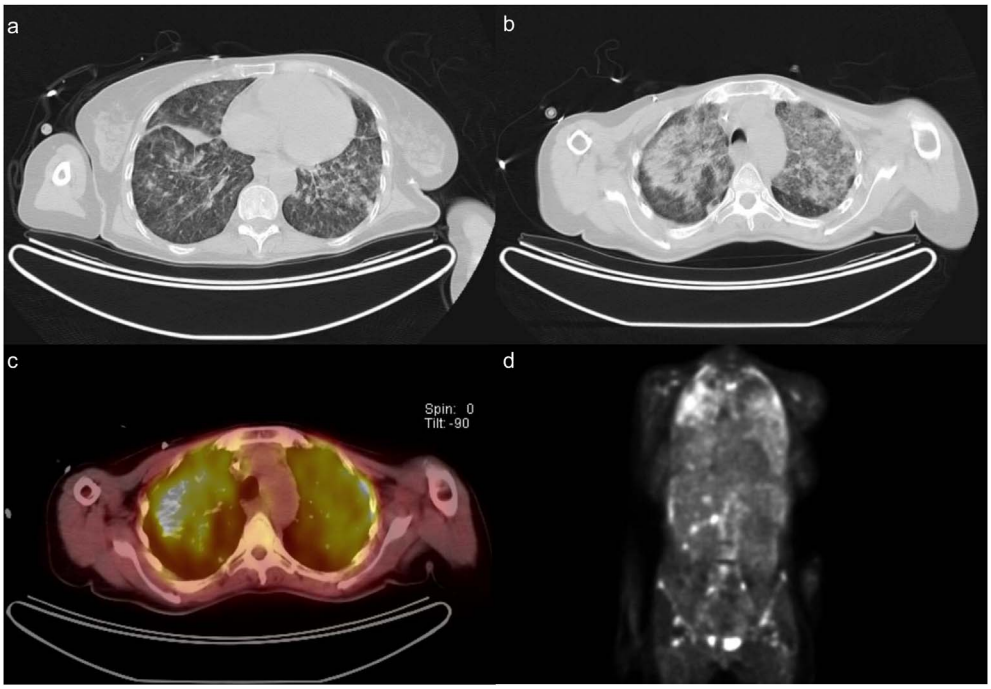


**Fig. 2.** Axial planes of thoracic non-enhanced-CT (a) and positron emission tomography (PET) (b–d) six weeks after CRS and HIPEC procedure. Fig. 2 displays extensive metastasis and inflammatory infiltrates in both upper lobes in different non-enhanced axial planes (a, b) and in PET-visualization (c). Fig. 2 d shows a sagittal view of the body. Next to the inflammatory alteration of both lungs, multiple metastases of the lungs, bones and bone marrow can be identified.

Retrospectively, neither signs of cardiac failure nor PH have been detected in the patient's medical history prior to the HIPEC procedure. She was non-smoking, able to hike 40 km in two days and covered 2000 m in height without dyspnea, discomfort or chest pain. Prior the reported hospitalization, she underwent multiple medical examinations (chest X-rays, electrocardiography, thoracic CTs), but none depicted signs of right ventricular failure or PH. Due to the good clinical condition, preoperative anesthesiological assessment did neither include echocardiography nor spirometry. Immediately after the HIPEC procedure the patient developed clinical and radiographic signs of an interstitial pulmonary edema that can be explained by liberal peri- and postoperative volume management and a major postsurgical capillary leakage, rather than by cardiac failure.

## 3. Discussion

### 3.1. HIPEC

We report the case of a 48-year-old woman who died of right ventricular and respiratory failure six weeks after multivisceral resection and HIPEC. Rapid aggravation of interstitial pneumonitis and PH could be unveiled as the underlying cause of death and confronted us with an unknown scenario within this clinical constellation. Providing critical patient selection and a strict safety regimen, CRS and HIPEC represent widely applied and well-established procedures in the treatment of different cancer entities like colon- and gastric cancer [4–7]. Compared to palliative surgery and/or systemic chemotherapy, evidence supports a beneficial effect of HIPEC in matter of disease-free and overall survival (with/without early post-operative intraperitoneal chemotherapy) [8–12]. If applied to selected patients with peritoneal carcinomatosis of gastrointestinal malignancies, a treatment-related mortality as low as 1.5% was described [13]. Current data revealed a HIPEC-associated mortality of 4.8%, which is still comparable to major gastrointestinal surgery [14]. Increased HIPEC-related morbidity compared to the standard surgical approach for the treatment of advanced gastric cancer (OR = 1.67, 95%-CI: 1.13–2.45, $p = 0.009$) was recently reported, while respiratory complications differed not significantly between both groups (surgery alone vs. surgery and HIPEC, $p > 0.05$) [15].

### 3.2. Pulmonary hypertension

Regarding the period of 6 weeks of good initial recovery after CRS and HIPEC, the patient's inconspicuous cardiac and pulmonary history as well as the rapid aggravation of the patient's clinical condition and cardio-pulmonary situation, raised suspicion onto a thromboembolic affection or an infectious cause. Low infectious laboratory values, normal body temperature, lack of infectious signs in the radiographic examinations in addition to unsuspicious microbiological findings did neither support the suspected diagnosis of severe infection nor did they explain the pronounced clinical status.

Cancer related thromboembolism represents a relevant complication of solid tumor diseases that worsens the patient's outcome if not recognized and treated adequate [16,17]. A retrospective single center study identified an age of > 40 years, advanced cancer stage, active chemo-therapy, use of erythropoetin for anemia and underdosage of thrombosis prophylaxis as risk factors for cancer related thromboembolism in patients suffering of solid tumor diseases [16]. The described patient met, except for the usage of erythropoetin and the underdosage of thrombosis prophylaxis, all of these risk factors. Despite the high-risk profile, extended radiographic imaging and laboratory tests ruled out an acute thromboembolic complication as cause for the rapid onset of PH. Moreover, approximately 25% of deceased cancer patients show tumor embolism in the pulmonary circulation leading to tumor migration, microangiopathy and subsequently also to PH [18]. Particularly associated with PH are gastric, breast, ovarial, pulmonary, renal and colon cancer entities. Nevertheless, no signs of tumor embolism as possible cause of a beginning chronic thromboembolic PH (CTEPH) could be detected within the presented patient. Based on these results, we sought for alternative underlying pathomechanisms explaining the further aggravating PH with consecutive respiratory and right ventricular failure of unknown origin. Considering the world health organization classification of PH [19], we searched without success for signs of venous occlusive disease, portopulmonary hypertension, congestive heart failure, chronic infectious diseases or genetic disorders leaving the differential diagnosis of acute pulmonary diseases or drug induced PH.

Initial thoracic CT showed extensive atypical interstitial and partly alveolar edema of the lung. These diagnostic findings were not

concordant to the severity and the development of the PH. Positron-emission-tomography (PET) presented a change of the pulmonary dissemination with extensive inflammatory activity in both upper lobes (Fig. 2 b–d). The institutional pulmonary radiological specialist evaluated these findings as pneumonitis, accordable to a drug induced interstitial pneumonitis (patchy ground glass opacities, reticular increased streaking, pleural effusions). The inflammatory pattern were not detectable directly after, but on day eight after admission to the hospital. Subsequently, possible drug related mechanisms leading to pulmonary inflammation and PH were examined.

### 3.3. 5-Fluorouracil

Because of symptomatic polyneuropathy, intravenous chemotherapy with Oxaliplatin and 5-FU was stopped after two cycles six months prior to the CRS and HIPEC procedure. The side effect profile of Calciumfolinat and 5-FU did neither indicate pulmonary complications, PH nor pulmonary fibrosis. Performing a literature search, we were not able to find information about pulmonary complications and/or side effects that are singularly connected to 5-FU or Calciumfolinat [search items: development PH, respiratory failure, pulmonary complications, complications + HIPEC, complications + CRS, connected to intravenous/intraabdominal 5-FU or Calciumfolinat; Databases: PubMed, Embase, Cochrane Library]. Already in 1979, Fielding et al. portrayed a lethal case of emerging interstitial fibrosis following intravenous application of 5-FU and Mitomycin [20]. After exclusion of other etiological factors, they stated a connection between the chemotherapy and the fibrosing alveolitis. Another case report describes the onset of an acute lung injury associated with systemic Oxaliplatin and 5-FU chemotherapy. Similar to the reported patient, an organizing diffuse alveolar damage pattern was found. Unfortunately, a differentiation between both chemotherapeutical drugs as the causing agent was not possible [21]. Chan et al. described a third case in which a combination of Oxaliplatin and 5-FU for intravenous chemotherapy was connected to symptomatic pulmonary fibrosis in a patient with preexisting asymptomatic interstitial lung disease [22]. A review of the literature indicated that 5-FU is only associated to pulmonary side effects when used as co-medication of Oxaliplatin or Mitomycin. While the pulmonary tissue appears not to be impaired by 5-FU, the cardiotoxic effects seem to be distinctively more significant, ranging from 7.6% up to 15% in patients with preexisting coronary artery disease [23]. These cardiotoxic effects seem to be based on endothelial damage and/or vasoconstriction of vascular smooth muscle cells. *In-vitro*-evidence (rabbits) shows a 5-FU-associated endothelium-independent vasoconstriction of aortic vascular smooth muscle cells [24]. Furthermore, Suedhoff et al. were able to show an arterial contraction (brachial artery) analogue to 5-FU application [25]. Polk et al. summarize the pathomechanisms leading to cardiotoxic effects of 5-FU as a result of endothelial injury followed by thrombosis, increased metabolism leading to energy depletion and ischemia, oxidative stress causing cellular damage and coronary artery spasm leading to myocardial ischemia [26]. Considering the aforementioned studies, 5-FU could possibly result in PH, if pulmonary vessels would be affected. But to our knowledge no data exists, which identified an isolated connection between 5-FU and pulmonary arterial endothelial damage and/or vasoconstriction.

### 3.4. Oxaliplatin

Oxaliplatin represents an established chemotherapeutical drug with an adverse side effect profile including peripheral sensory neuropathy, hematological toxicity, and allergic reactions [27]. When used for intravenous chemotherapy, Oxaliplatin is known, although infrequent, to cause severe pulmonary complications like interstitial pulmonary fibrosis [21,28–30] or pneumonitis [7,31–33]. But, a direct damaging effect of Oxaliplatin on lung tissue or vessels has yet not been identified. Previous studies suggest that therapy with Oxaliplatin can lead to a reduction of serum-levels of glutathione, which possibly results in oxidative stress of the pulmonary vessels leading to interstitial pneumonitis and pulmonary fibrosis [34,35]. Pulmonary fibrosis and grade IV pulmonary toxicity were reported in less than 1% of patients treated with Oxaliplatin [27,36]. Twenty-six descriptions of Oxaliplatin-related pulmonary toxicity have been described in the current literature, while sixteen of these cases (61.5%) were fatal [27]. Keldsen et al. investigated the pulmonary side effects in a prospective setting for patients with colorectal cancer and adjuvant Oxaliplatin therapy and showed only a small decrease in spirometric Tiffeneau's ratio (forced expiratory volume in one second/forced vital capacity ratio ($FEV_1$/FVC), $p = 0.03$), while neither other pulmonary parameters nor respiratory status worsened [37]. No other similar case descriptions or surveys of PH after HIPEC procedure with Oxaliplatin have been detected in the literature search [search items: development PH, pulmonary/respiratory failure, pulmonary/respiratory complications, complications + HIPEC, complications + CRS, connected to intravenous/intraabdominal Oxaliplatin; Databases: PubMed, Embase, Cochrane Library]. Overall, in consequence of the little existing data the extent and relevance of pulmonary toxicity of Oxaliplatin remains not quantifiable. The rare but potentially lethal side effects exhibit currently only few identified risk factors such as preexisting lung disease or smoking history [38]. In contrast to other chemotherapeutics like Bleomycin or Busulfan, that are known for their pulmonary toxicity, treatment guidelines for Oxaliplatin induced pulmonary complications are not available [39,40]. The wide use of Oxaliplatin, in mainly multidrug treatment regimens, complicates the differentiation of potential singular drug side effects. On the contrary, several case reports showed a resolution of the pulmonary complications after exclusion of Oxaliplatin from the intravenous chemotherapeutic drug regime [5,28,41]. Nevertheless the current data is connected to intravenous usage of Oxaliplatin and does not provide further information about its intraabdominal application in HIPEC patients [29–31,33,37,40,42,43]. Although the absorption of intraabdominal administered cytostatic drugs is very low, a certain amount is still systematically incorporated [10]. The reabsorption of Oxaliplatin might be facilitated by its high absorption rate in comparison to 5-FU even though it exhibits a higher molecular weight (molecular weight 397 g/mol (Oxaliplatin) vs. 130 g/mol (5-FU), area under the curve ratio of systemic vs. intraperitoneal resorption of 1:25 ml/min/1,73 $m^2$ (Oxaliplatin) and 1:250 ml/min/1,73 $m^2$ (5-FU)) [44]. Multivisceral surgery accompanied by HIPEC procedure generates a vast field of damaged tissue resulting in barrier disturbances and peritoneal leakage. These effects lead to significant variations of the peritoneal absorption and plasmatic Oxaliplatin concentrations as described in former studies [45–47]. In the presented case the operative procedure lasted over 10 hours with extensive surgical trauma, which might have led to relevant Oxaliplatin-absorption. In the context of systemic application, cumulative dose of Oxaliplatin does not appear to be a risk factor for following pulmonary complications, as these were observed after the first cycle of chemotherapy up to more than 12 cycles [41,48]. In our opinion, based on its side effect profile and a possible peritoneal reabsorption, Oxaliplatin is the most likely cause of pulmonary damage leading to PH in the presented patient, even though we are not able to exclude 5-FU or other drugs as relevant co-factors.

Moskovitz stated, that drug-induced PH is a diagnosis of exclusion, which remains a challenging task caused by an overlap of symptoms and the difficult retracing of the causative drug in a multi therapeutic regime [36]. The reported patient presented rapid structural pulmonary change after HIPEC procedure resulting in progressive PH and consecutive right ventricular impairment. Even though we were able to perform extended examinations, the time from the patient's diagnosis to her death was to short to prove our hypothesis of Oxaliplatin-induced lung damage with consecutive PH.

## 4. Conclusion

Rapid onset and progress of PH and interstitial pneumonitis, might be associated with Oxaliplatin-containing HIPEC therapy. Oxaliplatin-induced interstitial lung diseases should be considered for the differential diagnosis of respiratory disorders following HIPEC procedure. Further investigations of chemotherapeutical-induced side effects on the respiratory system are necessary as well as further experimental studies in order to clarify the underlying mechanisms of possible HIPEC-induced lung injury.

## Ethical approval

Ethical approval was not required for this case report presentation.

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## Author contribution

Writing the paper & data collection: Thomas S. Zajonz, Christian Koch, Emmanuel Schneck, M. Sander, W. Padberg, A. Hecker and R. Hörbelt.

## Conflicts of interest

The authors have neither financial disclosures nor conflicts of interest to report.

## Guarantor

Thomas S. Zajonz, E. Schneck, M. Sander.

## Consent

Informed consent to publish this case report was obtained from the patient. Patient's data was de-identified.

## Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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## List of abbreviations

| | |
|---|---|
| AT | Acceleration Time |
| BNP | Brain Natriuretic Peptide |
| CK | Creatine Kinase |
| CK-MB | Creatine Kinase Myoglobin |
| CO | Cardiac Output |
| CRP | C-reactive Protein |
| CRS | Cytoreductive Surgery |
| CT | Computer Tomography |
| CTEPH | Chronic Thromboembolic Pulmonary Hypertension |
| CVP | Central Venous Pressure |
| ET | Ejection Time |
| $FEV_1$/FCV | Forced Expiratory Volume in one Second/Forced Vital Capacity Ratio |
| HB | Hemoglobin |
| HIPEC | Hyperthermic Intraperitoneal Chemotherapy |
| OR | Odd's Ratio |
| PET | Positron Emission Tomography |
| PAD | Post-Admission Day |
| $PAP_{sys}$ | Systolic Pulmonary Artery Pressure |
| PCT | Procalcitonin |
| PH | Pulmonary Hypertension |
| TAPSE | Tricuspid Annular Plane Systolic Excursion |
| 5-FU | 5-Fluorouracil |

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