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3 **Development of stress-induced cardiomyopathy after cytoreductive**
4 **surgery and hyperthermic intraperitoneal chemotherapy**

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11 **Abstract**

12 Pseudomyxoma Peritonei, a massive mucinous peritoneal collection due to a rare
13 epithelial neoplasm, can be effectively treated with Cytoreductive Surgery and
14 Hyperthermic Intraperitoneal Chemotherapy (CRS-HIPEC).

15 A 43-year-old female, previously treated for mucinous ovarian carcinoma with CRS-
16 HIPEC, and total abdominal hysterectomy and bilateral salpingo-oophorectomy,
17 presented with new-onset abdominal distension and early satiety. She was diagnosed
18 with Pseudomyxoma Peritonei. After 48 hours of treatment with CRS-HIPEC, she
19 presented haemodynamically unstable with acute chest pain. Electrocardiogram showed
20 broad complex tachycardia with ST depression in leads V3-6. Severe systolic
21 dysfunction with Ejection Fraction (EF) of 20% along with severe pulmonary
22 hypertension, visualized on Echocardiography. A diagnosis of Stress-induced
23 Cardiomyopathy was established using InterTAK Diagnostic Score.

24 Patients with CRS-HIPEC have presented with Stress-induced Cardiomyopathy.
25 However, no specific relation between the two has been established. This case report
26 discusses Stress-induced Cardiomyopathy as a complication of CRS-HIPEC.

27 **Keywords:** Stress-induced; cardiomyopathy; Cytoreduction; Chemotherapy

28

29 **Introduction**

30 Stress-induced Cardiomyopathy, also known as Takotsubo Cardiomyopathy Syndrome
31 (TTS) is defined as temporary left ventricular dysfunction due to stress and/or surgery.⁽¹⁾

32 Pseudomyxoma Peritonei (PMP), a rare clinical condition which occurs in 1–2 people
33 in a million⁽²⁾ is characterized by massive amounts of mucous in the peritoneum mostly
34 due to a tumour of the appendix.⁽³⁾ Despite the slow spread, the long term survival rate
35 is 50% and 10%-30% at 5 and 10 years, respectively.⁽⁴⁾ The gold standard treatment of
36 PMP is Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS-
37 HIPEC)⁽³⁾ as it not only improves the quality of life but has been shown to have better
38 survival rates.⁽³⁾ A retrospective multicentre series of 2,298 patients, showed a 10-year
39 survival rate of 63% after CRS-HIPEC.⁽⁵⁾

40 However, this treatment can induce physiological and potentially pathological changes
41 causing stress-induced Cardiomyopathy which may lead to postoperative morbidity and
42 mortality. We present the case of a 43-year-old female, who developed stress-induced
43 Cardiomyopathy after undergoing CRS-HIPEC for PMP. this case report highlights that
44 stress-induced Cardiomyopathy is a complication of CRS-HIPEC.

45

46 **Case Report**

47 A 43 years old female presented at Shifa International Hospital, Islamabad on 3th March
48 2019 with complaints of abdominal swelling and early satiety. Upon taking her medical
49 and surgical history, she had experienced similar symptoms in the past and was
50 diagnosed with Mucinous Ovarian Adenocarcinoma. She underwent elective CRS-
51 HIPEC. She later developed metastasis which were treated by total abdominal
52 hysterectomy and bilateral salpingo-oophorectomy in August 2018. The patient had
53 received four cycles of neoadjuvantive and adjuvantive chemotherapy, each with
54 Carboplatin and Paclitaxel. However, she recently started developing notable abdominal
55 swelling and early satiety again.

56 On evaluation, she was alert and well-oriented individual , with a height of 162 cm and
57 weight 51 kg. Her abdominal CT scan showed findings that were typical of PMP with

58 the suggestion of rupture of appendiceal mucocole as the primary cause. However, no
59 pathology was found in her chest. Due to her current disease, she was again offered
60 CRS-HIPEC.

61 Preoperatively, she had good functional class and her preoperative blood test was within
62 the normal limit except for mild anaemia (Hb = 10.2 g/dl). Her electrocardiogram and
63 echocardiography showed sinus tachycardia and an ejection fraction of 55%.

64 She underwent CRS which included splenectomy, appendectomy, cholecystectomy,
65 excision of pelvic mass adherent to the bladder, excision and repair of the bladder and
66 peritonectomy. This was followed by HIPEC with Mitomycin 20 mg, at 42 °C for 90
67 minutes. The intraoperative blood loss was 2000 ml. She was transfused 750 ml of
68 packed red blood cells and six litres of crystalloids and 200 ml of Albumin. She
69 remained stable intraoperatively except for occasional episodes of tachycardia and a
70 need for low-dose norepinephrine infusion to support haemodynamic parameters.

71 After the surgery, the patient was extubated and shifted to Intensive Care Unit. After
72 forty-eight hours of surgery, she complained of chest pain and developed tachycardia,
73 hypotension, tachypnoea and decrease in oxygen saturation (SpO₂: 86% on room air).
74 Her 12-lead ECG showed broad-complex tachycardia and depression of ST segment in
75 leads V3-6. Her echocardiography (Table 1) showed severe systolic dysfunction with
76 EF of 20%, along with severe pulmonary hypertension. Her cardiac enzymes and BNP
77 levels (Table 2) were also raised.

78 She was started on norepinephrine at 0.04 µg/kg/min. Aspirin and clopidogrel were
79 administered. Enoxaparin 60 mg subcutaneous was given on the following day. Her
80 respiration was supported by Bilevel Positive Airway Pressure. Cardiology consult
81 recommended coronary angiography but was refused by the patient. Her condition
82 improved overtime and she was discharged on the seventh post-operative day. On 2-
83 weeks follow-up visit, her echocardiogram revealed an improvement in ejection fraction
84 to 45%. No other abnormalities were noted, and she was scheduled for regular follow-
85 ups.

86

87 **Discussion**

88 CRS-HIPEC involves removal of the PMP affected areas, peritoneum and other intra-
89 abdominal organs, followed by perfusion of heated chemotherapy agent at 42-43° C for
90 1-2 hours directly within the abdominal cavity. Broadly, the procedure includes three
91 stages: Exploration, Cytoreduction/debulking and Chemoperfusion. CRS has minimal
92 residual tumour and cytotoxicity is achieved by delivering chemotherapeutic agents
93 directly into the peritoneal cavity. ⁽⁶⁾

94 The morbidity after CRS-HIPEC can be either related to surgery or chemotherapy.
95 Chemotherapy effects wound healing and increases the risks of infectious
96 complications. The surgery-related morbidity includes abscess, fistula, anastomotic
97 leak, postoperative ileus, wound infection, bleeding, thrombosis, pulmonary embolism,
98 pleural effusion, pneumothorax, and cardiac arrhythmias. ⁽⁷⁾ However, there is no case
99 report showing a relationship between CRS-HIPEC and stress cardiomyopathy.

100 TTS on electrocardiogram may mimic acute coronary syndrome. It may also present
101 with raised myocardial enzymes even with no obstructive coronary artery disease.
102 However, coronary angiography is often normal or typically shows less than 50%
103 luminal stenosis. Most patients recover completely, and the severely reduced left
104 ventricular systolic function recovers over four to eight weeks. ⁽⁸⁾

105 Stress-induced Cardiomyopathy is predominant in females. Patients mostly present with
106 chest pain and dyspnoea. However, other more serious signs such as cardiogenic shock,
107 hypotension, arrhythmias, and cardiopulmonary arrest are relatively common. ⁽⁸⁾ TTS is
108 most significantly associated with an identifiable stressor, ranging from an emotional
109 stressful event without a physical component to a physical stressor. Typically, physical
110 stressors involve major surgery, orthopaedic trauma, exacerbation of obstructive
111 airways disease, malignancy, chemotherapy and infections. ⁽⁹⁾

112 In TTS, as compared to ACS, initially the troponin values are usually similarly raised,
113 however, the peak values are noticeably lower. There is only slight elevation in
114 creatinine kinase and a remarkable increase in the plasma BNP which continues to rise
115 till approximately 24–48 hours after symptom onset. ⁽¹⁰⁾

116 In order to correctly diagnosis Stress-induced Cardiomyopathy, the International
117 Takotsubo Registry provides clinicians with the InterTAK Diagnostic Score. According
118 to the scoring system, the predicted probability of TTS increases with the increasing
119 score points of a patient. There is a chance of less than 1%, if the patient has 30 score
120 points. Similarly, patients with 50 points are 18% and patients with more than 70 points
121 are 90% more likely to have TTS. ¹⁰⁾

122 In the present case, the patient had emotional stress, and physical stress, adding up to a
123 score of 62 points indicating more than fifty percent probability of TTS. Although the
124 mechanism of TTS for this patient was uncertain, its occurrence seems to be associated
125 with anaesthesia, surgery, post-operative pain, chemotherapy and excessive stress
126 inflicted by the outcome of this postoperative treatment. This patient had chest pain,
127 dyspnoea, T-wave inversion in leads V3-V5 on ECG, mildly elevated cardiac enzymes
128 and BNP levels, and akinetic mid antero-septum on echocardiography. All of which
129 leads to a diagnosis of stress-induced Cardiomyopathy.

130 As she had high predictive InterTAK diagnostic score and no pre-operative tests
131 indicating coronary artery disease, coronary angiography to rule out coronary artery
132 disease was not performed. In addition, all the post-operative blood investigations and
133 imaging studies established the diagnosis of stress-induced Cardiomyopathy.

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135 **Conclusion**

136 This case of a 43-year-old female highlights stress-induced Cardiomyopathy as a
137 complication of the gold standard treatment modality available for PMP. In this case
138 report, the diagnosis of stress-induced Cardiomyopathy was made using the InterTAK
139 Diagnostic Score, and factors related to the presentation, aetiology, associations and
140 management are identified to prevent morbidity and mortality associated with the
141 treatment modality.

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147 **Conflict of interest:** None to declare

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187 **Abbreviations**

188 ACS: acute coronary syndrome; AR: aortic regurgitation; BNP: Brain natriuretic
189 peptide; CAD: Coronary artery disease; CK-MB: Creatine kinase-MB; CMR:
190 Cardiovascular magnetic resonance imaging; CRP: C-reactive protein; CRS:
191 cytoreductive surgery; CT: computerized tomography; DVT: deep vein thrombosis;
192 ECG: electrocardiogram; Echo: echocardiogram; ESR: erythrocyte sedimentation rate;
193 Hb: Haemoglobin; HIPEC: hyperthermic intraperitoneal chemotherapy; LVOTO: Left
194 ventricular outflow tract obstruction; METs: metabolic equivalent; MR: mitral
195 regurgitation; PMP: Pseudomyxoma peritonei; POD: postoperative day; PR: pulmonary
196 regurgitation; RV: Right Ventricle; RWMA: regional wall motion abnormalities; SPO2:
197 peripheral capillary oxygen saturation; TR: tricuspid regurgitation; TTE: transthoracic
198 echocardiogram; TTS: Takotsubo cardiomyopathy syndrome

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203 **Table 1: Echocardiography reports**

Echocardiography reports	
Preoperative Echo	EF: 55%, Trace AR, TR, mild mitral valve prolapse with mild MR
ECHO on POD 2	EF = 20%, mid antero-septum is akinetic, severe pulmonary hypertension, mild MR, moderate TR, mild PR, severe cardiomyopathy
ECHO on POD 4	Normal left ventricular size with severe systolic dysfunction. Estimated EF = 25%. Mid anteroseptum is akinetic.
Echo on POD 14	EF =40%

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207 **Table 2: Cardiac enzymes and BNP levels**

	Immediately after the event	Six hours after the event	Nine days after the event
Cardiac troponin I (reference range in females upto 15.6 pg/mL)	555.9 pg/mL	7397.3 pg/mL	-
Creatine kinase MB (CK-MB) (reference range in females up to 3.4 ng/mL)	4.2 ng/mL	30.5 ng/mL	-
Brain natriuretic peptide (BNP) (reference range <100 pg/mL)	252.1 pg/mL	-	190 pg/mL

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