

## Prevention of Surge in Cytokines: Sjogren's Syndrome for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Gnanasekaran Srinivasan<sup>1</sup>, Kirthiha Govindaraj<sup>2</sup>, Ameena Mohammed<sup>3</sup>

### How to cite this article:

Gnanasekaran Srinivasan, Kirthiha Govindaraj, Ameena Mohammed/Prevention of Surge in Cytokines: Sjogren's Syndrome for Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy/Indian J Canc Educ Res 2022;10(2):97-100.

### Abstract

Pseudomyxoma peritonei is treatable with newer surgical modalities like cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC), and the anesthetic management can be challenging. In our case, the perioperative management was further complicated by the presence of Sjogren's syndrome which has its own anesthetic implications. This may be the first reported case of anesthetic management of HIPEC in a patient having Sjogren's syndrome along with its perioperative considerations include fluid management, stable hemodynamics, thermoregulation, electrolyte balance, intraoperative massive fluid shifts, ventilatory management, avoidance of renal toxicity and suppression of cytokines release plays a major role in the management in this patient.

**Keywords:** Sjogren's Syndrome; Hyperthermic; Chemotherapy; Stable hemodynamics; cytokines release plays.

### INTRODUCTION

Pseudomyxoma peritonei (PMP) is a rare disease that originates usually from an appendiceal mucinous epithelial neoplasm. The relationship between the CRS (cytoreductive surgery) +HIPEC (hyperthermic intraperitoneal chemotherapy) and Sjogren's syndrome, is that the combined effect on flaring up of inflammatory cytokines associated with the surgery and the condition as well. Hence, the perioperative concerns in Sjogren's

syndrome patients undergoing this surgery were innumerable including avoidance of stress response associated with surgery and anesthesia, optimal fluid management, stable hemodynamics, thermoregulation, coagulation, electrolyte balance, and avoidance of nephrotoxicity secondary to chemo therapeutic drugs.<sup>1,5</sup>

### CASE REPORT

A 48 year old female patient with recurrent episodes of abdominal pain, loss of weight and appetite was admitted for evaluation. On examination, abdominal distension along with hepatomegaly was present. Contrast enhanced computed tomography of abdomen revealed multiple septations in the right iliac fossa and pouch of Douglas with a scarring in the surface of liver. Eventually patient was diagnosed as pseudomyxoma peritonei secondary to appendicular neoplasm and hence planned for CRS+HIPEC surgery. She was a known case of primary Sjogren's syndrome, diagnosed 3 years

**Author Affiliation:** <sup>1,2</sup>Assistant Professor, <sup>3</sup>Junior Resident, Department of Anesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, 605006, India.

**Corresponding Author:** Kirthiha Govindaraj, Assistant Professor, Department of Anesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, 605006, India.

**E-mail:** drkirthiharaj@gmail.com

**Received on:** 25.11.2022

**Accepted on:** 11.12.2022

ago when she had complaints of dryness of mouth and right sided parotid swelling. Salivary gland scintigraphy confirmed parotid and submandibular gland sialadenitis. An ophthalmologic examination was done in view of suspicion of Sjogren's syndrome and ocular sicca was confirmed. Immunoassay showed anti-nuclear antibody (ANA) of 4+, but C3, C4 and Rheumatoid factor were normal. Further diagnosis was confirmed with an anti-rho and anti-LA antibody, and the patient was on oral Hydroxychloroquine and topical pilocarpine and moisol for the eyes. She did not have any joint involvement and the DEXA scan was normal. Patient also had hypergammaglobulinemia and hypoalbuminemia which is not a general finding in pseudomyxoma patient. Further work up was planned for the same post surgery. There were no episodes of flare up in the last 3 years.

Preoperatively, ERAS protocol was followed for the patient with counselling, anaemia correction, high protein diet, regular 45 mins of walking per day, incentive spirometry, and prophylactic thromboprophylaxis. Along with peptic ulcer prophylaxis, paracetamol 500 mg per oral was given. In the operation theatre, standard monitors were attached; epidural catheter was placed at T10-T11 space. Rapid sequence induction and intubation was done with intravenous fentanyl 100 mcg, propofol 100 mg, succinylcholine 100 mg. Central venous cannulation and arterial cannulation were done to monitor CVP and invasive arterial pressure. Intraoperatively, patient was started on 20% albumin at 10 ml/hr, which was continued postoperatively for 48 hrs. Epidural infusion of 0.125% bupivacaine was initiated intraoperative for analgesia and to mitigate the stress response. The patient required noradrenaline support at 0.02 to 0.1 mcg/kg /min to maintain stable hemodynamics, within few hours of starting the surgery Tranexemic acid 1 gm and Dexamethasone 4 mg were given. She was ventilated with low tidal volume (330ml), volume controlled ventilation to maintain end-tidal CO<sub>2</sub> of 35-40 mmHg. An ocular tear drop was instilled throughout the intraoperative period to prevent dryness of the cornea. Patient required 4 units of PRBC and 4 units of FFP intraoperative except albumin. Urine output was maintained at 0.5-1 ml/kg/hr during cytoreductive phase, 2ml/kg/hr during HIPEC phase, and 1 ml/kg/hr at the end of surgery<sup>5</sup>. Temperature was maintained with forced air warmers, warm IV fluids, IV fluid warmer (despite the measures, temperature reduced up to 34.5°C) during cytoreductive phase and cold irrigation through nasogastric tube, ice packs, cold IV fluids during HIPEC phase

(temperature increased to the maximum of 37.8°C). HIPEC was done with mitomycin, doxorubicin and oxaliplatin according to Coliseum technique.<sup>1</sup> Stable hemodynamics was maintained throughout the procedure, IV fluid management was targeted according to the urine output and pulse pressure variation <12%. Though patient hemodynamics and urine output was maintained, patient developed metabolic acidosis with high lactate levels (4mmol/L) at the end operative period, without the need for noradrenaline support at the end of surgery, hence patient was extubated on the next day. Epidural infusion was continued with 0.125% bupivacaine + 2 mcg/cc fentanyl at 5 ml/hr for 48 hrs and with paracetamol thereafter. Patient was discharged on the 10th postoperative day with further follow-up in surgical oncology OPD.

## DISCUSSION

Primary peritoneal neoplasm, gynaecological or gastrointestinal malignancies with peritoneal metastasis, appendicular neoplasm with pseudomyxoma peritoni were associated with the poor prognosis.<sup>1</sup> As truly said by Dr. Paul Sugarbaker, these malignancies were treatable after the invention of heated loco-regional chemotherapeutic agents following the surgical removal of visible tumor.<sup>1,4</sup> Though primary epithelial neoplasm of the appendix were rare, 1/3rd of the lesions were epithelial mucinous neoplasm's which progresses to pseudomyxoma peritoni.<sup>2</sup> CRS involves stripping of macroscopic disease with visceral and parietal peritoneum, along with resection of organs, while HIPEC involves exposure to high peritoneal concentrations of chemotherapeutic agents with limited systemic absorption.<sup>4</sup>

Sjogren's syndrome is one of the most common chronic systemic autoimmune disorder with the overall prevalence of 0.1-0.4% in the general population, with female predominance of 9:1.3,6 The clinical hallmarks were dryness of the cornea and conjunctiva (keratoconjunctivitis sicca) and dry mouth (xerostomia) secondary to lymphocytic infiltration of lacrimal and salivary glands respectively.<sup>3</sup> Treatment includes immunosuppressant, and our patient was on hydroxychloroquine and symptomatic management for keratoconjunctivitis sicca and parotid gland involvement. The anesthetic implications of Sjogren's includes strict ocular protection with corneal humidification, avoid respiratory dryness by humidifying the gases, careful administration of the drugs (induction agents, hypnotics and

local anesthetics) with invasive blood pressure monitoring to avoid hemodynamic instability because of the possibility of autonomic dysfunction. Avoid parasympatholytic and anticholinergic drugs, whereas chronic medications have to be continued until the morning of surgery. The enlarged parotid and submandibular glands may make the mask ventilation difficult. Laryngoscopy and intubation are complicated by xerostomia, poor oro-dental hygiene, temporomandibular joint arthritis and crico-arytenoid joint involvement. Preoperative fiberoptic assessment helps to plan intubation strategies.

Our patient had Peritoneal Carcinomatosis Index (PCI) score of 17. If the PCI is higher, the prognosis becomes worse.<sup>1,4</sup> However in case of PMP patients, the approach is aggressive and found to have excellent outcome despite the PCI is very high and disease free survival does not depend on the PCI score in these patients.<sup>4</sup> The pathogenetic mechanisms underlying these immunological disorders is an appropriate and excessive immunological reaction by the patients auto-antibodies<sup>4,6</sup> and also dysregulated cytokine network, reflected by the local and systemic over expression of pro-inflammatory cytokines, and absent or low levels of anti-inflammatory cytokines present in Sjogren's syndrome.<sup>8</sup> Cytokine release happens secondary to inflammation produced by the level of surgical stress, the amount of dissection during CRS and the chemotherapeutic agents used in HIPEC.<sup>7</sup> In our case, added to the surgical inflammation, associated Sjogren's syndrome can cause flare up of inflammatory cytokines and increased capillary permeability resulting in decrease in oncotic pressure that results in hemodynamic instability. In our case, it was overcome by adequate epidural analgesia to reduce the stress response and blood loss, use of systemic steroid intra-operatively and paracetamol during preoperative and intraoperative period to reduce the inflammation and cytokine surge.

Further, noradrenaline infusion was started intraoperative, early enough to shift the blood from splanchnic circulation to central circulation, stable hemodynamics and prevent the blood loss while preserving intestinal villi microcirculation.<sup>5,9</sup> Studies have shown that noradrenaline has no detrimental effects on microcirculatory blood flow and tissue oxygenation in the intestinal tract. Hence continuous infusion increases the systemic vascular resistance to prevent the detrimental effects of compromised tissue perfusion especially in high risk patients and also reduces the fluid overload. Though we started noradrenaline infusion, still our

patient required 9 litres altogether like crystalloid, colloid, blood and blood products during the surgery.

Fluid management was done according to the hourly urine output, hemodynamics and the pulse pressure variation. IV fluid requirement > 20ml/kg/hr can result in increased morbidity and mortality and needs to be avoided.<sup>5</sup> Our patient required albumin infusion for two days postoperatively. As we did not have access to TEG, coagulation profile was done preoperatively, clinically by surgeons during intraoperative period, and postoperatively by repeating the coagulation profile. EtCO<sub>2</sub> was maintained at normal levels according to timing of hypothermic and hyperthermic phase. Though diaphragmatic stripping can result in delayed extubation<sup>4</sup>, we could able to extubate our patient on the first postoperative day and her length of hospital stay was 10 days. CRS-HIPEC requires analgesia from T6 to lower lumbar segments. And the perioperative coagulopathy, hemodynamic instability and infectious complications that may occur during CRS-HIPEC have raised concerns about the safety of epidural analgesia. Though the study by Bell et al caution the use of epidural due to the incidence of epidural abscess, however the study by Balakrishnan did not find any complications. The effect of epidural on surgery is to provide adequate analgesia, decreased opioid requirement, decreased blood loss and early extubation.

## CONCLUSION

Managing the Sjogren's syndrome patient for CRS with HIPEC is a real challenge and it requires the multidisciplinary approach along with surgeon, immunologists, anesthesiologists and the intensivist. Important perioperative task is to not to overload, and to suppress the flare up of cytokines secondary to extensive surgery as well as Sjogren's syndrome itself, along with respective surgical considerations of CRS and HIPEC.

## REFERENCES

1. Mishra R, Sharma K, Barpande J, Kumari N, Mehta H. Anaesthetic Management of Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC): A True Challenge To an Anaesthetist. *Journal of Current Medical Research and Opinion*. 2020;03(07):503-507.
2. Smeenk RM, Velthuisen MLFV, Verwaal VJ, Zoetmulder FAN. Appendiceal neoplasms and pseudomyxoma peritonei: A population based study.

3. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. *Clinical Epidemiology*. 2014;6:247-255.
4. Balakrishnan KP, Survesan S. Anaesthetic management and perioperative outcomes of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: A retrospective analysis. *Indian J Anaesth* 2018;62:188-96.
6. Solank SL, Mukherjee S, Agarwal V, Thota RS, Balakrishnan K, Shah SB, Desai N, Garg R, Ambulkar RP, Bhorkar NM, Patro V, Sinukumar S, Venketeswaran MV, Joshi MP, Chikkalingegowda RH, Gottumukkala V, Owusu-Agyemang P, Saklani AP, Mehta SS, Seshadri RA, Bell JC, Bhatnagar S, Divatia JV. Society of Onco-Anaesthesia and Perioperative Care consensus guidelines for perioperative management of patients for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). *Indian J Anaesth* 2019;63:972-87.
7. Renuka R. Anesthetic Management of a Rare Case of Primary Sjogren's Syndrome for a Gynecological Surgery. *Indian Journal of Anesthesia and Analgesia*. 2020;7(1):191-194.
8. Babazade R, Sun Z, Hesler BD, Sharma A, Makarova N, Dalton JE, and Turan A. The Association Between Sjögren Syndrome and Adverse Postoperative Outcomes: A Historical Cohort Study Using Administrative Health Data. *Anesthesia and Analgesia*. 2015; 121(5):1222-1230.
9. Roescher N, Tak PP, Illei GG. Cytokines in Sjogren's syndrome: potential therapeutic targets. *Ann Rheum Dis*. 2010;69(6).
10. Fan CN, Yang SJ, Shih PY, Wang MJ, Fan SJ, Tsai JC, Sun WZ, Liu CM, Yeh YC. Comparing effects of intraoperative fluid and vasopressor infusion on intestinal microcirculation. *Scientific reports*. 2020;10:19856.

