



## General anesthesia in a patient with multicentric Castleman's disease -a case report-

Hee Won Son, In Young Huh, Sang Hyun Lee, An Suk Kim, Se Hun Park, and Dae-Young Kim

*Department of Anesthesiology and Pain Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea*

Castleman's disease (CD) is a rare lymphoproliferative disorder of undetermined etiology. Unicentric Castleman's disease is confined to a single lymph node; it is usually asymptomatic though sometimes has local manifestations related to mass effects. In contrast, multicentric Castleman's disease (MCD) typically presents with lymphoid hyperplasia at multiple sites; it is associated with systemic symptoms and abnormal laboratory findings, with a less favorable prognosis. In case of anesthesia in CD, an exhaustive preanesthetic evaluation is essential to identify associated clinical manifestations which may influence the management of the anesthesia. Perioperative careful monitoring and proper anesthetic management are both important. We report a case of general anesthesia with anesthetic management in a patient with MCD that has not been documented in the literature.

**Key Words:** General anesthesia, Multicentric Castleman's disease.

Castleman's disease (CD) is a rare polyclonal lymphoproliferative disorder. In 1956, Dr. Benjamin Castleman first described a series of 13 cases involving mediastinal lymph node hyperplasia [1]. CD is histologically classified as the hyaline vascular (HV) type, the plasma cell (PC) type, or the mixed type [2,3], and clinically it is classified as unicentric (localized) CD (UCD) or multicentric (diffuse, systemic) CD (MCD). UCD is often associated with the HV type histologically and is usually mediastinal

and asymptomatic, whereas MCD is usually associated with the PC type or the mixed type histologically and shows an aggressive and relapsing course with systemic manifestations [3,4]. Because a histopathologic examination is necessary to confirm a diagnosis of CD, a generous specimen, generally an excisional biopsy, is required [5]. Therefore, CD patients often undergo resective or diagnostic surgery. The proportion of UCD is high in surgical cases of CD [6]. The disease is usually suspected after an examination of images before surgery and the diagnosis is confirmed from a biopsy after the surgery. There has been one reported case of combined spinal-epidural anesthesia on a patient diagnosed with UCD [7], but there have been no other cases reported on general anesthesia with anesthetic management of patients diagnosed with MCD with systemic manifestations. Thus, we aim to be the first to present such a case.

### Case Report

A 52-year old male patient, 177 cm in height and weighing

Corresponding author: Hee Won Son, M.D., Ph.D.  
Department of Anesthesiology and Pain Medicine, Ulsan University Hospital, 877, Bangeojinsunhwando-ro, Dong-gu, Ulsan 682-714, Korea  
Tel: 82-52-250-7248, Fax: 82-52-250-7249  
E-mail: hwson@hanmail.net

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61 kg, was admitted to the hospital emergency room. He had experienced general weakness starting 10 days earlier and complained of right upper quadrant pain that had started 4–5 days before being admitted. The patient had been diagnosed with PC-type MCD five years earlier, which was confirmed by clinical findings; by computed tomography (CT) scans which had shown multiple lymph node enlargements in the neck, axillary, mediastinal, abdominal, and pelvic space; and by a right axillary lymph node biopsy under local anesthesia. After eight cycles of chemotherapy, the patient entered into complete remission, but there had been a loss to follow-up. Afterwards the patient had no history of taking any specific drugs, and he had a smoking history of 20 pack-years. A contrast-enhanced CT scan was obtained, which found acute calculous cholecystitis, lymphadenopathy with multiple enlarged nodes in the abdomen and pelvis, splenomegaly, bilateral pleural effusion, and small amounts of ascites in the cul-de-sac. The patient was scheduled for surgery, but during the preoperative evaluations, a blood test found anemia, thrombocytopenia, lymphopenia, and azotemia. The echocardiography showed findings of stress-induced cardiomyopathy (ejection fraction [EF] = 43%). Therefore, it was decided that the patient's underlying condition must be improved before having surgery. Accordingly, percutaneous transhepatic gallbladder drainage was first performed. A CT scan was also taken, which showed multiple lymph node enlargements which aroused suspicion of the recurrence of CD and prompted an evaluation. Serum immunofixation electrophoresis showed polyclonal hypergammaglobulinemia. In a bone marrow study, plasmacytosis was observed. Laboratory findings of reductions in his platelet count, hemoglobin (Hgb), lymphocyte, total cholesterol, and albumin and increases in his international normalized ratio (INR), blood urea nitrogen, creatinine, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and vascular endothelial growth factor (VEGF) were observed. These were findings that fit the clinical manifestations of a MCD patient, leading to the conclusion that CD had recurred. However, the serological test for human immunodeficiency virus (HIV) was negative. The patient was started on chemotherapy again. From day 7 after being admitted, pulmonary edema worsened due to the exacerbation of the stress-induced cardiomyopathy (EF = 25%), the patient complained of dyspnea, and oliguria occurred due to the worsening of the azotemia. As a result, after aggressive treatment including four days in the intensive care unit (ICU), the patient's clinical signs gradually improved. Twenty-three days after being admitted, the echocardiography showed normalization of the left ventricular systolic function (EF = 68%), as well as improvements in his pulmonary edema and azotemia. However, despite transfusions of leukocyte-poor and irradiated packed red blood cells (RBC) and platelets along with fresh frozen plasma (FFP), there was no significant improvement in the blood lab values,

with Hgb at 3.8–11.6 g/dl, the platelet count at 31,000–132,000 / $\mu$ l and INR remaining at 1.32–2.02. After one month of hospitalization, an elective laparoscopic cholecystectomy was planned for the patient.

An exhaustive preanesthetic evaluation was performed. Before surgery, a blood transfusion of packed 2 units of RBC, 8 units of platelets, and 4 units of FFP was given, which improved the blood lab values (Hgb 9.0 g/dl, platelet 78,000 / $\mu$ l, INR 1.41). Although there were signs of mild dyspnea, there was no cough or sputum but there was abdominal distension found during a physical examination. A chest X-ray showed a waning pattern of ill-defined consolidation in both lungs. There were no rales or wheezing according to a chest auscultation. A pulmonary function test could not be performed because the patient was in a bed-ridden state. The electrocardiogram (ECG) findings were normal. A thoracic CT scan showed no findings of a mediastinal mass.

Without being premedicated, the patient was transferred to the operating room where ECG, a pulse oximetry monitor and bispectral index monitors were applied. After performing a modified Allen's test to assess the collateral blood flow to the hand, a 22 G catheter was inserted in the left radial artery for continual arterial pressure monitoring and arterial blood gas sampling. Moreover, for close fluid management and less-invasive circulatory monitoring while the patient was under anesthesia, a catheter was connected to a FloTrac<sup>TM</sup>/Vigileo<sup>TM</sup> monitor (Edwards Lifesciences, Irvine, CA, USA). Before preoxygenation, the patient's room air arterial blood gas analysis (ABGA) results were as follows: pH, 7.53; PaCO<sub>2</sub>, 27 mmHg; PaO<sub>2</sub>, 65 mmHg; HCO<sub>3</sub><sup>-</sup>, 22.6 mEq/L; BE, -0.1 mEq/L; SaO<sub>2</sub>, 95 %; Hgb, 8.8 g/dl; and Hct, 26%. His electrolytes were in normal ranges. General anesthesia was induced with intravenous thiopental sodium (100 mg), 2% lidocaine (40 mg), etomidate (10 mg), cisatracurium (14 mg), and remifentanyl (0.15  $\mu$ g/kg/min), and a tracheal tube was inserted orotracheally. General anesthesia was maintained with sevoflurane (1.5–3 vol%), O<sub>2</sub> (1.5 L/min), air (1.5 L/min), and remifentanyl (0.05  $\mu$ g/kg/min). For continuous central venous oxygen saturation (ScvO<sub>2</sub>) monitoring and for an aggressive administration of fluid, blood, and drugs in case of an emergency, a triple lumen PreSep<sup>TM</sup> central venous oximetry catheter (Edwards Lifesciences, Irvine, CA, USA) was inserted via his right internal jugular vein. A foley catheter was not inserted. Using a Vigileo<sup>TM</sup> monitor, cardiac output, stroke volume, stroke volume variation (SVV), systemic vascular resistance, and ScvO<sub>2</sub> were continuously monitored during perioperative fluid and circulatory management. After starting the surgery, the Calot's triangle had severe inflammation and adhesion, making dissection impossible. Consequently, the surgery was switched to an open cholecystectomy. Perioperative drainage of the ascites was about 2 L. Cisatracurium of 2 mg

and ephedrine of 5 mg were additionally administered intravenously. Vital signs monitored during the surgery were a BP of 105–150/50–85 mmHg, HR of 82–110 beats/min, and oxygen saturation of 100%. The parameters displayed on the Vigileo™ monitor all remained in their normal ranges without sudden changes. The bispectral index remained in the range of 32–39. The last measured ABGA results during surgery were as follows: pH, 7.39; PaCO<sub>2</sub>, 38 mmHg; PaO<sub>2</sub>, 141 mmHg; HCO<sub>3</sub><sup>-</sup>, 23 mEq/L; BE, -2 mEq/L; SaO<sub>2</sub>, 99 %; Hgb, 7.8 g/dl; Hct, 23%; Na, 138 mmol/L; K 3.8 mmol/L; and Ca<sup>2+</sup>, 0.97 mmol/L. The surgery was uneventful, and the duration of the operation and anesthesia were 1.5 and 2.5 h. There was no significant blood loss, and infused crystalloid fluid amounted to 1,100 ml. Once anesthesia was terminated, the patient awakened smoothly and the tracheal tube was removed. The patient was transferred to the ICU for close monitoring. The patient's postoperative vital signs and laboratory findings were satisfactory, and the next day the patient was moved to the general ward. The patient was kept at the hospital for continuous chemotherapy for CD. Approximately one month after the surgery, the patient developed a cough and sputum. In an evaluation, fungal pneumonia was suspected and treatment was started. However, the patient's condition rapidly deteriorated. Despite aggressive treatment including ventilator care in the ICU, the patient expired three days into the treatment.

## Discussion

Although CD was discovered more than 50 years ago, its pathophysiology has not been fully elucidated. Currently, the putative etiologic roles of cytokine interleukin-6 (IL-6) and human herpes virus-8 (HHV-8) have been highlighted. In western countries, HHV-8 is frequently associated with the etiology of MCD, especially in HIV, and the disease prognosis is poor [3,4,8,9]. A proposed unified model of the pathophysiology of MCD is that HHV-8-infected cells secrete a viral homolog of IL-6, which in turn enhances the production of VEGF, further inducing angiogenesis inside the tumor and human IL-6 production by endothelial cells. IL-6 excess results in lymphovascular proliferation and inflammatory systemic manifestations. In HHV-8<sup>-</sup> CD patients, undefined factors can trigger IL-6 production [4].

CD is classified into three histological subtypes: the HV, PC, and mixed types [2,3]. Clinically, CD is also separated into UCD and MCD on the basis of the lymph node lesions involved [3-5]. Recently, new classifications have been proposed focusing on the associations between clinical and pathological findings [9,10]. The discovery of a strong correlation between centricity and histopathology has made such nosological classifications possible [10].

CD is typically presents as a mediastinal mass and primarily involves the lymphatic tissue, but it may also occur in virtually any area of the organism (the neck, axilla, larynx, parotid gland, lungs, retroperitoneum, mesentery, kidney, pancreas, pelvic cavity, muscle, pericardium, central nervous system [CNS] and vulva) [5,7,11]. UCD is the most common form of CD; it is confined to a single lymph node chain or area, is usually the HV type, and is often asymptomatic. The enlarged nodes may be identified either incidentally or through symptoms related to local mass effects [3]. MCD is a less common and a more aggressive form. It is usually the PC type or the mixed type. Systemic manifestations, sometimes severe and life-threatening, are common. Frequent symptoms are fever, night sweats, weakness, fatigue, anorexia, weight loss, skin rash, multifocal lymphadenopathy, hepatosplenomegaly, renal dysfunction, and pulmonary diseases such as lymphocytic interstitial pneumonia. Seizures and other central and peripheral nervous system symptoms can also be seen. In severe cases, ascites, pleural effusion, and peripheral edema are common. These patients show a wide range of laboratory abnormalities, such as anemia; thrombocytopenia; thrombocytosis; leukocytosis; polyclonal hypergammaglobulinemia; hypoalbuminemia; hypocholesterolemia; bone marrow plasmacytosis; and increases in liver enzymes, creatinine, ESR, CRP, and IL-6 levels [4,5,8].

Centricity (MCD), histopathology type (PC), gender (male), age (> 37 years), and the presence of symptoms in HIV<sup>-</sup> patients and with HIV infection influence poor outcomes. MCD usually appears in older patients [10]. The outcome of MCD can be fatal due to the progression to severe pancytopenia, fulminant infections, and multiorgan failure. Also, MCD patients, especially with the HHV-8-related forms are at high risk for developing lymphomas, Kaposi's sarcoma, and POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome [4,12].

The mainstay of treatment for UCD is complete surgical resection. Local recurrence has rarely been reported. Radiotherapy could be a valuable option when complete resection is not possible. However, for MCD, surgical debulking is seldom curative and generally achieves only a transient improvement. Therefore, MCD patients almost always need systemic therapy [4,5,10]. MCD may require a corticosteroid treatment, chemotherapy, targeted immunotherapy, antiviral medications, or the use of antiproliferative regimens [4,12].

With regard to a systemic therapy for MCD, there is still no consensus regarding a gold standard therapeutic approach due to the rarity and heterogenous nature of MCD [3]. Moreover, patients diagnosed with CD who undergo general or regional anesthesia for surgery are extremely rare. Therefore, there is no clinically proven principle for anesthetic management in CD patients. The clinical signs and symptoms of CD patients vary,

ranging from asymptomatic to life-threatening. Therefore, anesthesia should be differentiated and performed according to the characteristics of the manifestations of the individual.

In a preanesthetic evaluation, the various systemic manifestations and laboratory abnormalities of the individual should be fully grasped. Knowing the CD's centricity and histopathologic type can help in predicting the patient's symptoms, disease severity, and outcome associated with the nosological classification. In such cases, a serological test for HIV and HHV-8 and a serum IL-6 level check can also help. In the present case, the patient had multifocal lymphadenopathy and various clinical manifestations similar to his condition five years earlier; therefore, the recurrence of PC-type MCD was diagnosed without an excisional rebiopsy. However, unfortunately, no tests for HHV-8 infection or serum IL-6 level were performed.

With a CT or MRI scan, the infiltrated area of the lymphadenopathy and the presence of a mass and its location can be examined. In CD, the lung and pericardium can be involved and can be accompanied by pleural effusion. Therefore, performing an echocardiography and a pulmonary function test before the surgery can be helpful. If necessary, additional tests can be performed, and problems that may arise during anesthesia can be predicted in advance. If accompanied with anemia and thrombocytopenia, a blood transfusion is decided upon after considering the degree of perioperative bleeding risk. Hypoalbuminemia and elevated liver enzymes and creatinine are aggressively corrected. Also, if there are associated problems in the patient that could present a risk during anesthetic management, such as azotemia or pulmonary edema as in the patient in the present case, the patient should recover through an aggressive preoperative treatment to be safe.

The choice of regional anesthesia is based on type of surgery and the absolute or relative contraindications. Coagulopathy or other bleeding tendencies, symptoms or mass involving CNS, infection at the site of injection, and bacteremia or sepsis are considered as contraindications. CD is rarely reported as a form of a spinal epidural, subdural extramedullary, and meningeal mass in the CNS lesion. Motor-sensory neuropathy is a common neurological manifestation. It can be caused by cord compression [7,13]. In the present case, there were no lesions involving the CNS, but because there was thrombocytopenia, an increase in the INR, and in that the case involved abdominal surgery, general anesthesia was decided upon.

CD usually arises as a solitary mass that is commonly found in the mediastinum. During the induction of general anesthesia, airway obstruction and cardiovascular collapse due to compression of the heart or major vessels are the major complications. Therefore, in such cases, careful continuous monitoring of gas exchange and hemodynamics is required. Complaints of cough or dyspnea should alert the clinician to the possibility of airway

obstruction upon the induction of anesthesia. Anesthetic induction can be inhalation induction or intravenous titration of propofol, maintaining spontaneous ventilation. In certain situations, awake intubation may be required. When muscle relaxation is needed, the feasibility of positive-pressure ventilation is first checked before infusing muscle relaxants [14].

Cervical lymph nodes are the most common sites after the mediastinum for single lymph nodes or chain involvement. If there is any infiltration in the neck, larynx, or parotid gland or if the patient is accompanied with steroid-induced facial-truncal obesity, intubation could be difficult and cause danger in ventilation. Therefore, experienced staff and the proper equipment must always be immediately available [3,7,11].

There is a high risk of infection in CD. MCD in particular can progress to severe pancytopenia and fulminant infection [4, 12]. The patient in the present case was also accompanied with lymphopenia and was again undergoing chemotherapy. Therefore, aseptic manipulation must be strictly adhered to during the anesthetic procedure for CD patients.

In MCD, occasionally renal complications such as renal amyloidosis, glomerulonephritis, interstitial nephritis, and thrombotic microangiopathy have been reported [12]. Also, because renal dysfunction including elevated creatinine can be present, perioperative hypovolemia and the use of nephrotoxic agents must be avoided. Drugs that are excreted by the kidney can have prolonged action duration; therefore, the drug dose needs to be titrated. The metabolism and elimination of cisatracurium appear to be independent of renal or liver failure. The patient in the present case received treatment for azotemia before the surgery. Accordingly, cisatracurium was chosen for muscle relaxation. On rare occasions, CD is associated with myasthenia gravis, most likely due to possible autoimmune pathology [11]. Hence, in such cases, muscle relaxants should be used with careful monitoring.

In MCD, renal dysfunction is common, and in severe cases it is accompanied with ascites, pleural effusion, and peripheral edema. As a result, much attention should be given to volume management. The patient here was treated before surgery for pulmonary edema and azotemia and was drained of 2 L of ascites during surgery; he clearly needed careful fluid administration. For the perioperative monitoring of fluid responsiveness and circulatory management, we used a less-invasive circulatory monitoring system, the Vigileo™ monitor, which can be used in combination with FloTrac™ and PreSep™ sensors. SVV precisely predicts intravascular hypovolemia, and the continuous monitoring of ScvO<sub>2</sub> enables an evaluation of the adequacy of tissue oxygenation [15]. The Vigileo™ monitor provided reliable information for the perioperative management of the risk in the patient in this case report.

The patient experienced no events during anesthesia, and the

surgery was successful. However, one month later, the patient experienced an infection suspected to be fungal pneumonia, and he suddenly expired. It was not found that the infection was related to his anesthetic management practices. Considering that the patient's condition suddenly worsened one month after surgery, it is believed that the two combined factors of MCD and vulnerability to infection led to the poor prognosis.

In summary, CD is rarely seen in anesthesia management,

but MCD especially is accompanied with various clinical manifestations related to CD that affect anesthetic management. Consequently, with a thorough preoperative assessment, problems that can arise during anesthesia should be predicted while during anesthesia, anesthetic management and monitoring must be meticulous. Also, it should be noted that there is a high risk of complications such as postoperative infections.

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