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Case Report

Severe pancytopenia and coagulopathy discovered during anesthesia after pre-anesthetic evaluation
- A report of two cases -

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Background: Pre-anesthetic evaluation is an important aspect of perioperative patient management. However, anesthesiologists often encounter challenges during anesthesia due to conditions that are not detected during pre-anesthetic evaluations.

Case: Case 1 involved a 74-year-old female patient scheduled for cranioplasty and meningioma excision. Severe pancytopenia was detected during anesthesia. Cranioplasty was only performed, the surgery was terminated, and drug-induced pancytopenia was diagnosed and treated. The pre-anesthetic test results were normal, except for anemia. Case 2 involved a 71-year-old male patient who discovered large ecchymosis during general anesthesia preparation in the operating room for choledochal cyst surgery. Surgery was canceled to evaluate the bleeding tendency, and acquired coagulation factor VIII deficiency was diagnosed and treated. The pre-anesthetic tests were normal, except for prolongation of the activated partial thromboplastin time.

Conclusions: Abrupt hematologic and hemostatic changes may occur during anesthesia even though pre-anesthetic evaluation findings are normal.

Keywords: Anesthesia; Coagulation factor deficiency; Coagulation factor VIII; Pancytopenia; Pre-anesthetic evaluation.

The purpose of a pre-anesthetic evaluation is to establish an optimal perioperative anesthesia plan by identifying risk factors, including unrecognized diseases or disorders, that may affect perioperative anesthesia management and assessing already known diseases. Pre-anesthetic evaluations should be considered for their potential benefits and adverse effects. While they may improve the safety and effectiveness of anesthesia management, their potential adverse effects include injuries, discomfort, inconvenience, delay in surgery, and additional costs [1]. Pre-anesthetic evaluations include reviews of medical records, patient interviews, physical examination, and preoperative tests, including electrocardiography, chest radiography, and laboratory tests, when indicated. However, preoperative tests may increase risks and costs, and test results often do not significantly alter anesthesia management in relatively healthy patients. Therefore, the guidelines for pre-anesthetic or preoperative evaluations by the American Society of Anesthesiologists, European Society of Anesthesiology, and National Institute for Health and Clinical Excellence (NICE) recommend that pre-

operative tests are performed based on the grade of surgery, physical status of the patient, and underlying diseases [1-3].

Despite the pre-anesthetic evaluations, anesthesiologists often encounter serious situations during anesthesia due to diseases or conditions that are not identified before anesthesia. Massive bleeding and subsequent complications may occur during surgery when a bleeding tendency is not detected during the pre-anesthetic evaluation. In addition, the patients can be life-threatened without adequate patient monitoring, intravenous access, and preparation for transfusion. We report two cases of severe pancytopenia and acquired coagulation factor deficiency that were not detected during pre-anesthetic evaluations.

CASE REPORT

This report was approved by the Institutional Review Board (IRB) of our hospital, and the requirement for informed consent was waived (IRB no. E2022-15).

Case 1

A 74-year-old female patient was scheduled to undergo cranioplasty and removal of a meningioma under general anesthesia. The patient was diagnosed with subarachnoid hemorrhage and meningioma, and underwent emergency craniectomy and cerebral aneurysm clipping 3 weeks ago. The subarachnoid hemorrhage was caused by an aneurysmal rupture of the left posterior communicating artery. In addition, meningioma of the right frontal lobe revealed by computed tomography in the emergency room. She had no history except for hypertension, and the complete blood count (CBC) conducted five days before surgery showed a hemoglobin (Hb) of 8.9 g/dl, hematocrit (Hct) of 26.7%, platelet count (PLT) of 314,000/μl, and white blood cell count (WBC) of 7,000/μl. Noninvasive blood pressure, electrocardiography, and pulse oximetry were monitored after the patient was admitted to the operating room. Propofol and remifentanil were used for the induction and maintenance of anesthesia. After endotracheal intubation, an arterial cannula was inserted into the left radial artery for continuous invasive blood pressure measurements. Additionally, a central venous catheter was placed in the right subclavian vein. Arterial blood gas analysis (ABGA) and CBC were performed to establish the initial baseline status of the patient during surgery after a skin incision in the scalp for cranioplasty. Pancytopenia was confirmed based on the severe decrease in the Hb to 6.5 g/dl, Hct to 19%, PLT to 13,000/μl, and WBC to 2,000/μl. We immediately notified the surgeon of the pancytopenia and repeated the CBC to rule out errors. Hb and PLT had further reduced: Hb, 5.7 g/dl; Hct, 17.2%; PLT, 10,000/μl; and WBC, 2,100/μl. Blood pressure and heart rate were stable at 110/50 mmHg and 65 beats/min, respectively, at the time of laboratory tests. No abnormal bleeding was observed at the surgical site. In addition, there were no signs of unexpected acute bleeding, such as abdominal distension or hematuria. We decided to proceed with cranioplasty because the operation proceeded after the skin incision, and there was no abnormal bleeding at the surgical site. However, craniotomy was required to remove the brain tumor because the meningioma was located on the right side, and the risk of bleeding and postoperative infection increased. Therefore, the meningioma removal was canceled. The estimated blood loss during surgery was 700 ml. Five units of packed red blood cells (PRBC) were transfused. A crystalloid solution (1,500 ml) and colloid solution (500 ml) were administered during surgery. The patient's vital signs were intraoperatively stable. The postoperative laboratory test finding in the intensive care unit showed Hb at 9.9 g/dl, Hct at 29.3%, PLT at 11,000/μl, and WBC at 6,300/μl. Sepsis, disseminated intravascular coagulation, and drug-induced pancytopenia were evaluated in consultation with the hematologist. Normocytic normochromic anemia, normal WBC, and thrombocytopenia were observed on a peripheral blood smear. This was bicytopenia with a restored WBC count. Schistocytes were not observed. The coagulation tests showed activated partial thromboplastin time (aPTT; normal range 23.5–32.5 s) of 35.4 s, prothrombin time (PT; normal range 8.3–10.4 s) of 10.4 s, and an international normalized ratio (INR; normal range 0.93–1.16) of 1.14. The fibrinogen was 255 mg/dl (normal range 193-412 mg/dl) and the D-dimer was 1.44 μg/ml (normal range 0–0.5 μg/ml). The vital signs were stable during the perioperative period, and there were no symptoms or signs of bleeding or infection. Considering the results of the laboratory tests and the condition of the patient, drug-induced pancytopenia was suspected. Levetiracetam and ceftriaxone were presumed to be the causes. Levetiracetam was administered after cerebral aneurysmal clipping to prevent epileptic seizures, and ceftriaxone was used five days before surgery to treat urinary tract infection. Ceftriaxone was discontinued, and levetiracetam was replaced with valproate. Periodic laboratory tests were performed intermittently with the transfusions of PRBC and platelet concentrates (PC) (Table 1). The bicytopenia recov-

Table 1. Complete Blood Count for Case 1

Timing	Hemoglobin (mg/dl)	White blood cell count (cells × 10^3/μl)	Platelet count (cells × 10^3/μl)
1st operation (pre)	11.3	8.1	279
1st operation (post)	7.9	15.9	149
2nd operation (pre)	8.9	7.0	314
Intraoperation 1	6.5	2.0	13
Intraoperation 2	5.7	2.1	10
2nd operation (post)	9.9	6.3	11
POD 1	9.7	4.1	18
POD 3	9.7	4.2	12
POD 5	9.9	4.4	20
POD 7	9.2	4.5	43
POD 9	8.8	6.6	91
POD 14	8.6	6.1	295

The first operation is cerebral aneurysmal clipping, and the second operation is cranioplasty. POD: postoperative day.

Table 2. Coagulation Test and Factor VIII for Case 2

Variable	aPTT (s)	PT (s)	PT (%)	INR	Factor VIII (%)
Normal range	23.5–32.5	8.3–10.4	70–127	0.93–1.16	50–150
Preoperation	43.3	9.5	90	1.04	
Postoperation	75.7	10.7	72	1.17	3
POD 1	54.5	10.1	80	1.11	5
8 days after steroid treatment	36.9	9.5	87	1.05	60
15 days after steroid treatment	26.4	9.0	99	1.00	> 100

aPTT: activated partial thromboplastin time, PT: prothrombin time, INR: international normalized ratio, POD: postoperative day.

ered 14 days after the surgery, and the patient was discharged without meningioma removal.

Case 2

A 71-year-old male patient was scheduled for the excision of a choledochal cyst under general anesthesia. He was hospitalized with abdominal pain and evaluated for disease. He was taking medications, including aspirin, for hypertension and diabetes. The laboratory tests performed 7 days before surgery showed that only the aPTT increased to 43.3 s; the PT was 9.5 s and the INR was 1.04. The CBC and serum chemistry results were normal. There were no specific findings from the pre-anesthetic patient interview or physical examination a day before surgery. Bruises in the intravenous access site and a large ecchymosis involving the back, waist, and buttocks were observed while verifying the identity of the patient and attaching the patient monitoring device after admission to the operating room. After discussing the condition of the patient with the surgeon, we decided to examine and treat the bleeding tendency before surgery. The CBC results were normal. The coagulation test showed aPTT of 75.7 s, PT of 10.7 s, and INR of 1.17. In addition, the plasma mixing test showed transient normalization of aPTT, coagulation factor VIII level of 3% (normal range: 50–150%), and coagulation factor IX level of 92% (normal range: 50–150%). The coagulation factor VIII antibody was positive. The patient was diagnosed with acquired coagulation factor VIII deficiency and transferred to the Department of Hemato-Oncology. The coagulation test results and coagulation factors were normalized approximately four weeks after treatment with steroids, and the patient was discharged after surgery. Table 2 summarizes the results of the coagulation and coagulation factor VIII tests.

DISCUSSION

Pancytopenia and acquired coagulation factor deficiency are uncommon but they can cause severe bleeding when surgery is performed without detecting them. Laboratory tests, such as CBC and coagulation tests, are essential for their diagnoses. However, laboratory tests are recommend-

ed "selectively" rather than "routinely" during pre-anesthetic evaluation because they can lead to adverse effects and additional costs, and abnormal results often do not significantly change the anesthetic management. According to the guidelines of the American Society of Anesthesiologists, Hb and Hct are measured for old age or a history of liver disease, anemia, hemorrhage, or other hematologic diseases. Coagulation tests should be performed for patients with bleeding disorders, renal impairment, and hepatic impairment and those who use anticoagulants [1]. The NICE guidelines recommend that preoperative tests should be guided by the American Society of Anesthesiologists physical status (ASA) of the patient and surgical grade (minor, intermediate, or major surgery). CBC is recommended for all patients with ASA I–IV before major surgery, and it should be considered before intermediate surgery when patients with ASA III–IV have underlying diseases. Coagulation tests are recommended as needed for patients with ASA III–IV for both intermediate and major surgeries [3].

In our hospital, pre-anesthetic evaluation includes the review of pertinent medical records, patient interviews, and physical examinations. It is conducted a day before elective surgery. In contrast with the recommendations of the American Society of Anesthesiologists and NICE, electrocardiography, chest radiography, and laboratory tests are performed routinely; the laboratory tests include CBC, serum chemistry, and coagulation tests. In general, when elective surgery is scheduled, preoperative tests are performed at the outpatient clinic, and further consultation or examination depends on their results.

Therefore, the duration between the preoperative tests and surgery may differ from weeks to months. Both patients were evaluated after hospitalization. The most recent laboratory tests were performed on the fifth and seventh days before surgery. Nevertheless, we did not detect pancytopenia or acquired coagulation factor deficiency during the pre-anesthetic evaluation.

For case 1, the patient had normal CBC results except for anemia preoperatively. No symptoms or signs suggestive of pancytopenia, such as fever, palpitation, or bleeding, were observed. In this patient, it can be inferred that pancytopenia developed after the preoperative tests. Levetiracetam and ceftriaxone are presumed to be causes [4-6]. Drug-induced pancytopenia is a rare condition; however, various drugs, including nonsteroidal anti-inflammatory drugs, anti-epileptics, anti-thyroid drugs, rheumatologic drugs, and antimicrobials, have been implicated. Myelosuppression and consumption or destruction of peripheral blood may underlie drug-induced pancytopenia [7]. Levetiracetam induces pancytopenia via bone marrow suppression. Most cytopenia cases occur within 24 hours to a few days after using levetiracetam, but it may be first detected several months after drug use [8]. Ceftriaxone-induced cytopenia is a rare condition. It is known to induce drug-induced immune thrombocytopenia rather than pancytopenia [9]. A drug-dependent antibody binds to the glycoprotein of the PLT membrane and activates PLT consumption in drug-induced immune thrombocytopenia. Anesthesiologists recognize that various drugs can cause hematologic disorders, but it is difficult to consider these during pre-anesthetic evaluations. As with case 1, it may be impossible to diagnose cytopenia that develops after laboratory tests during the pre-anesthetic evaluation because tests are not repeated without significant changes in the condition of a patient. In this case, pancytopenia was confirmed in patient evaluation during anesthesia. We place the arterial cannula for invasive blood pressure monitoring and laboratory tests, such as ABGA, during the surgery when a significant amount of bleeding is expected, and intraoperative tests are conducted early to establish a baseline for the laboratory tests. In case 1, CBC was performed along with ABGA because the Hb reduced to 8.9 g/dl in the preoperative test. These early examinations during anesthesia can help detect unpredictable changes in the condition of the patient.

The acquired coagulation factor VIII deficiency detected in Case 2 is predominantly idiopathic, but it may be caused by autoimmune or cancerous diseases [10]. It is classified as severe (< 1%), moderate (1–5%), or mild (> 5%), depending on the activity of coagulation factor VIII. The aPTT was prolonged 2–3 times during the coagulation test. The degree and frequency of bleeding vary with the coagulation factor activity. Spontaneous hemorrhage within the muscle or joint and life-threatening hemorrhage may occur in severe. Spontaneous bleeding is uncommon, but bleeding after trauma often occurs in moderate. The coagulation factor activity in this patient was 3%, which was moderate. In addition to the extensive ecchymosis, bruises were also found at the site where intravenous cannulation was attempted or failed. If bleeding tendencies, such as bruising and ecchymosis, were more carefully investigated without ignoring the increased aPTT detected by the coagulation test, acquired coagulation factor deficiency may have been confirmed during the pre-anesthetic evaluation via additional examinations.

Pancytopenia and acquired coagulation factor deficiency

can cause severe intraoperative bleeding, which can seriously compromise patient safety. When an unexpected bleeding tendency that is not detected during the pre-anesthetic evaluation occurs during surgery, the anesthesiologist should perform CBC and coagulation tests to confirm cytopenia or coagulopathy. If significant cytopenia or impairment of coagulation is present, the surgeon should be immediately notified and the continuation of the surgery should be discussed. The surgical plan may be changed or the surgery may be discontinued when these disorders are detected before anesthesia induction or at an early stage of the surgery. However, treatment is mandatory for cases requiring surgery. PRBC and PC are transfused in pancytopenia, and the transfusion of fresh frozen plasma or cryoprecipitates and PRBC is required to correct coagulation impairment. Coagulation factor deficiency is treated by supplementing the deficient coagulation factor.

Pancytopenia or aggravation of coagulopathy may occur after preoperative tests for pre-anesthetic evaluation. These findings may not be confirmed during pre-anesthetic patient interviews and physical examinations. Performing preanesthetic evaluations continuously until the induction of anesthesia and conducting intraoperative tests early may help to detect these diseases and prevent risks during anesthesia. Therefore, anesthesiologists should be aware that unexpected changes in patient conditions may occur during perioperative period, and the safety of patients should be ensured by conducting continuous patient evaluations.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Conceptualization: Hyun Joo Heo. Data curation: Hyung Gu Cho, Geonbo Kim. Writing - original draft: Yu Yil Kim. Writing -review & editing: Ji Hye Lee.

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