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CLINICAL REPORT

Perioperative management for a patient with chronic pancytopenia: a case of aplastic anemia with persistent neutropenia following preoperative administration of G-CSF

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Abstract The patient, a 62-year-old male suffering from aplastic anemia for 6 years, was admitted in order to undergo laparoscopic cholecystectomy for cholecystitis. Results of laboratory tests at the time of admission revealed pancytopenia: white blood cell count, 1.94×10^3/μl (neutrophil count, 1.23×10^3/μl); red blood cell count, 2.09×10^6/μl; Hb 7.5 g/dl; and platelet count, 3.7×10^4/μl. The patient received supportive therapy prior to surgery, including blood transfusion of red blood cells, platelets and granulocyte colony-stimulating factor (G-CSF). On the day of surgery, the white blood cell count increased to 3.93×10^3/μl (neutrophil count, 2.75×10^3/μl). Surgery ended with no intraoperative complications, but neutropenia progressed and persisted postoperatively: the neutrophil count decreased to 180/μl at its lowest and stayed at about 400–600/μl. This suggests the possibility that repeated preoperative administration of G-CSF may lead to the depletion of granulocyte precursor cells and thus cause harm. Although the patient fortunately achieved a favorable outcome without severe infection, this case is a stark reminder of the difficulties involved in perioperative supportive therapy for patients with chronic pancytopenia.

Keywords Chronic pneutropenia · Supportive therapy · G-CSF · Aplastic anemia · General anesthesia · Surgical stress

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Introduction

Aplastic anemia is characterized by chronic pancytopenia with diminished hematopoietic precursors in bone marrow [1]. Anemia, a hemorrhagic tendency and a susceptibility to infection are all risks associated with the perioperative period, and patients need supportive care, including transfusions of blood and G-CSF. So far, there have been few reports and no guidelines on perioperative management for patients with chronic pancytopenia. At the same time, it is anticipated that the number of pancytopenic patients undergoing anesthesia will increase, given increasing patient ages and the advances made in therapies for intractable blood disorders and malignant tumors.

Here, we report a patient with aplastic anemia who developed postoperative neutropenia, which was probably triggered by preoperative supportive therapy.

Case report

The patient, a 62-year-old male suffering from aplastic anemia for 6 years, was admitted in order to undergo laparoscopic cholecystectomy for cholecystitis. His height was 169 cm and his body weight was 60.3 kg. He was diagnosed at another hospital with aplastic anemia at age 56, and he received the oral anabolic hormone metenolone, sulfamethoxazole trimethoprim, an infusion once every 3 weeks of two units of red cell concentrate–leukocyte reduced (RCC-LR), and subcutaneous injections of 300 μg (5 μg/kg) granulocyte colony-stimulation factor (G-CSF) twice a week. He had no known hemorrhagic tendency in his daily activities, and no history of platelet transfusions.

Laboratory tests at the time of admission showed pancytopenia: white blood cell count of 1.94×10^3/μl,

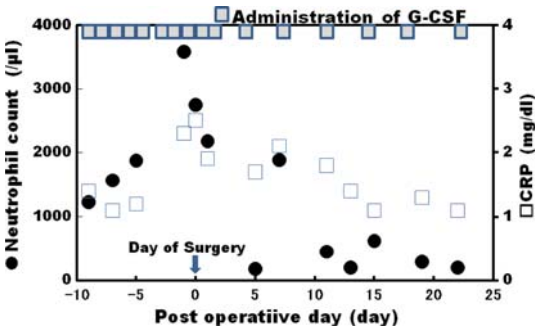

Fig. 1 Changes in the neutrophil count and C-reactive protein (CRP) during the perioperative period. Injections of G-CSF 300 μg were given almost daily from 8 days prior to surgery to postoperative day 2, a total of 10 days. Subsequently, 300 μg was given twice a week, the same amount that he received before hospital admission, but neutropenia persisted with a neutrophil count of about 400–600/μl. Plasma concentrations of CRP showed no big changes perioperatively

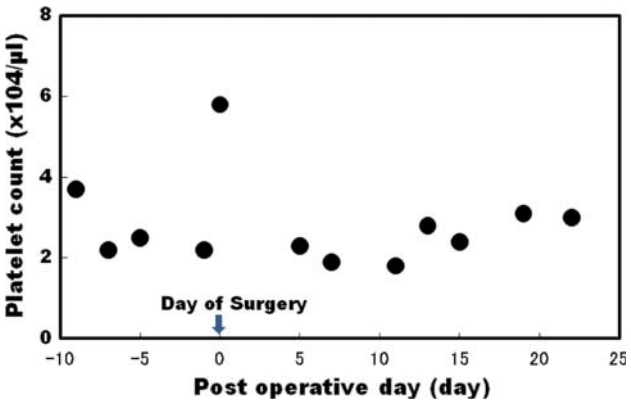

Fig. 2 Changes in the platelet count during the perioperative period. Ten units of platelet were transfused during the 5 days prior to surgery, and he received 15 units and 10 units on the day before surgery and just before surgery, respectively. There were no significant differences between the preoperatrive and the postoperative platelet counts, with a count of about 3.0×10^4/μl maintained

neutrophil count of 1.23×10^3/μl, red blood cell count of 2.09×10^6/μl, hemoglobin 7.5 g/dl, and a platelet count of 3.7×10^4/μl. Irregular antibodies (anti-E and anti-C) were also detected. The activated partial thromboplastin time (APTT) was 27.8 s, and the prothrombin time–international normalized ratio (PT-INR) was 1.11; both were within the normal range.

Supportive therapy for pancytopenia was performed from the preoperative period. Specifically, 300 μg of G-CSF were given daily for a total of 7 days from 8 days prior to surgery until the day itself to treat the neutropenia. On the day of surgery, his white blood cell and neutrophil counts increased to 3.93×10^3/μl and 2.75×10^3/μl, respectively (Fig. 1). Four units of RCC-LR were transfused during the 5 days prior to surgery, 10 units of platelet concentrate (PC) during the 5 days before surgery, and 15 units on the day before surgery, and 10 units prior to operation on the day of surgery (Fig. 2). The laboratory tests performed on the day of surgery showed a red blood cell count of 2.55×10^6/μl, hemoglobin 8.7 g/dl, and a platelet count of 5.8×10^4/μl. Cefazolin (2 g/day) was given on the day of surgery as prophylactic antibiotic therapy.

General anesthesia was induced with propofol 100 mg, fentanyl 50 μg, remifentanil 0.25 μg kg^{-1} min^{-1}, and vecuronium 6 mg, and tracheal intubation was performed. Anesthesia was maintained using sevoflurane 1.5–2% and remifentanil 0.2 kg^{-1} min^{-1}. There was no obvious hemorrhagic tendency during surgery, and blood loss was 10 ml. Surgery was 91 min, and the duration of the anesthesia was 122 min. The patient had no postoperative incision infection or hemorrhage. On postoperative day (POD) 1, 2 units of RCC-LR and 10 units of PC were transfused, and the interval between administrations of G-CSF shifted from successive days to every 2 or 3 days. Subsequently, Hb was maintained at around 8 g/dl, and the platelet count was maintained at about 3×10^4/μl, with no deterioration observed compared to those seen before hospital admission. However, the neutropenia gradually progressed, and on postoperative day (POD) 5 the neutrophil count reached its lowest level at 180/μl. The patient was given 5 μg/kg G-CSF, and while the neutrophil count increased to 1800/μl on POD 7, it decreased to 450/μl at POD 11 and the neutropenia persisted despite the administration of the same dose at the same interval as before hospital admission. He fortunately developed no serious infection throughout the postoperative period, but his period of hospitalization was extended. On the 19th day after surgery he was discharged and followed up as an outpatient, receiving G-CSF once every 3 days. His neutrophil count remains low (around 400/μl) and he remains in good condition. His plasma concentration of C-reactive protein (CRP) showed no big changes perioperatively (Fig. 1).

Discussion

Aplastic anemia is a bone marrow failure disorder that is diagnosed based on findings of pancytopenia and low cell production in the bone marrow [1]. Anemia, a hemorrhagic tendency, and a vulnerability to infection associated with chronic pancytopenia are causes of clinical concern, and perioperative supportive therapy is important. Patients with aplastic anemia show chronic stable thrombocytopenia and a hemorrhagic tendency is unlikely to occur until a platelet count of below $5–10 \times 10^3$/μl is attained. Our patient has never shown a bleeding tendency with his platelet count of about 3.0×10^4/μl.

For patients without any risk factors, a threshold for platelet transfusion of $5 \times 10^3/\mu l$ is recommended [2]. However, for chronic pancytopenic patients who are scheduled for surgery, there are no guidelines that suggest an adequate platelet count. In leading guidelines, a platelet count of $>5 \times 10^4/\mu l$ is recommended for general surgery and $>10 \times 10^4/\mu l$ for cardiac surgery or neurosurgery, but these guidelines are experience-based and do not consider patients with chronic thrombocytopenia [2–4]. Concerning the timing of preoperative platelet transfusions, since approximately 30% of transfused platelets are sequestered in the spleen, and the lifespan of platelets is short, they should be transfused immediately before surgery. However, it may be important to transfuse platelets several days before the operation in order to rule out platelet refractoriness. In particular, there is a high risk of platelet refractoriness if the patient has a history of platelet transfusion or is positive for anti-erythrocyte antibody [4, 5]. To evaluate the effectiveness of platelet transfusion, the corrected count increment (CCI) is calculated from the results for blood sampled 24 h following transfusion [= increase in transfused platelet count (/μl) × body surface area (m^2)/platelet count in transfused blood volume ($\times 10^{11}$)], and if the CCI is <4500/μl 24 h later, there is a high probability of platelet resistance [4]. If platelet resistance is observed, it is necessary to explore the causes, including immunological mechanisms such as the presence of anti-HLA antibodies or anti-platelet antibodies, as well as non-immunological mechanisms such as fever, drug-induced mechanisms, DIC and splenomegaly [2, 4].

In the patient reported here, the platelet count was $2.2 \times 10^4/\mu l$ in blood sampled on the day before surgery, whereas the platelet count was $5.8 \times 10^4/\mu l$ in blood sampled at 7 a.m. on the day of surgery after a 10-unit transfusion, and the CCI had risen to 30400 μl. However, since the platelet count was predicted to drop below $5 \times 10^4/\mu l$ during the operation, an additional 10-unit transfusion was given just before surgery. As a result, there were no hemostatic difficulties during surgery, and the platelet count was still $3.2 \times 10^4/\mu l$ on the day after surgery.

Red blood cell transfusions for anemia in recent years have focused not on raising the Hb level to within the normal range but rather on maintaining a sufficient oxygen supply [6, 7]. In patients with chronic anemia, even if the Hb level is depressed, the oxygen supply to peripheral tissues can be maintained by raising the tissue blood flow volume, cardiac output, or by increasing erythrocyte 2,3-diphosphoglycerate (2,3-DPG), which make the oxygen–hemoglobin disassociation curve shift to the right. Furthermore, in addition to the general side effects of transfusions, regular red blood cell transfusions carry the risk of causing iron overload disorders such as hemochromatosis, so unnecessary transfusions should be avoided. Ideally, factors such as oxygen supply and demand and venous oxygen saturation should be assessed, but in actual clinical practice the Hb level is usually used as an indication for transfusion. Although an Hb level of less than 6–8 mg/dl has been suggested as a threshold for RCC transfusion in the perioperative period, this threshold cannot be simply applied to patients with chronic anemia because of their compensatory mechanism [6–8].

Neither are there clear guidelines for the perioperative management of neutropenia. Only a few surgerical cases of patients with neutropenia have been reported, and the effects of preoperative administration of G-CSF are controversial [9–11]. In general, there is no risk of infection if the neutrophil count is >1500/μl, and only a very slight risk of severe infection at 1000–1500/μl, while an absolute neutrophil count of less than 500 is considered to be vulnerable to any opportunistic infection. However, the relationship between neutrophil count and infection incidence during the perioperative period remains unclear. Actually, the administration of G-CSF is not strongly recommended in cases of chemotherapy-induced afebrile neutropenia [12]. In addition, it is still not known whether or to what extent compensatory mechanisms function in chronic neutropenia, and it is possible that chronic neutropenic patients may be at a lower risk of infection than acute neutropenic patients, including chemotherapy patients.

G-CSF induces a switch in T-cell cytokine production from a Th1 profile (IL-1β, IL-12, IFN-γ, IL-18, TNF-α) to a Th2 (IL-1Ra, soluble TNF-Rs) response [13]. This feature is also known as compensatory anti-inflammatory response during the postoperative period, and so plasma concentrations of CRP are at very low levels perioperatively in this case.

In the case reported here, neutropenia progressed and persisted despite the postoperative administration of G-CSF. Since anesthetics such as nitrous oxide that can suppress bone marrow were not used in our case and the duration of anesthesia was short, rather than being the effect of the anesthetic, the neutropenia was caused by the depletion of granulocyte precursor cells as a result of the intensified supportive treatment before surgery. It is well known that surgical stress can induce transcriptional upregulation of G-CSF by activating transcriptional factors such as NF-κB (nuclear factor kappa B) [14]. As an analysis of the plasma G-CSF concentration was not done during the perioperative period, the theory regarding the transcriptional upregulation of G-CSF is purely speculative. If we wanted to check for the possibility of the depletion of neutrophil precursor cells, an examination of bone marrow aspiration and a biopsy are absolute prerequisites. This means that the prophylactic administration of G-CSF on consecutive days had a negative aspect.

Fortunately, the patient did not develop a serious infection, but the persistent neutropenia led to a higher risk of infection and a longer period of hospitalization. This means that future cases should be studied to determine whether the intensified administration of G-CSF contributes to reducing the risk of infection during the perioperative period for patients with afebrile neutropenia. If needed, the appropriate dose, the method of administration, and the tapering method should also be investigated. In aplastic anemia, immunosuppressive therapy using cyclosporine A and glucocorticoid is sometimes administered. However, there is the possibility that aplastic anemia shifts to myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) after surgical stress or G-CSF exposure. Young et al. found a statistically significant association between G-CSF and risk of MDS/AML [15]. Similar findings were reported in a review of 48 adults with aplastic anemia, in which MDS developed in 4 of the 13 patients on G-CSF administration. Patients with highly abnormal stem cells caused by aplastic anemia may be more likely to relapse and develop MDS/AML due to G-CSF. This therapy still has many difficulties due to the possibility of malignant transformation with G-CSF.

As described above, the appropriate perioperative supportive treatment for patients with chronic pancytopenia remains to be established. It is true that severe pancytopenia and associated complications do have a risk of patient fatality, but we should recognize that excess transfusion including RCC-LC, PC and G-CSF may also do harm.

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