Acute exacerbation of cold agglutinin disease during operation

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Cold agglutinin, an autoantibody that combines with the red blood cell (RBC) carbohydrate antigen, is known to trigger hemolysis with agglutination at temperatures of 0–4°C [1]. Cold agglutinin combined with RBC in a peripheral body exposed to a cold environment returns to the center of the body and combines with the complement; these processes form the mechanism for chronic cold agglutinin disease. However, these processes can result in acute aggravation due to stimuli such as infection and trauma [2]. The authors experienced hemolysis during an operation in a patient with cold agglutinin disease although his temperature was maintained above 35.6°C.

A 67-year-old male patient diagnosed with bladder cancer was scheduled for a radical cystectomy with ileal conduit formation. He had been diagnosed with idiopathic cold agglutinin disease 20 years earlier. Hematologic conditions were stable without any medication. Hemoglobin was measured as 6.9 g/dl 2 days prior to the surgery. After 3 units of leukocyte-depleted RBC were transfused, the hemoglobin level increased to 9.9 g/dl. The cold agglutinin titer was 1 : 8192 and total bilirubin was 2.9 g/dl before the surgery.

On the day of the surgery, the temperature of the operation room was raised to its maximum of 30°C. An esophageal stethoscope with a temperature probe was inserted after induction to read the core body temperature (BT), and a skin temperature probe was attached to the forehead to read the peripheral BT. The body of the patient, excluding the site of surgery, was covered in cotton blankets, and 2 air warmers were used. A normothermic (37°C) intravenous fluid administration set was used to elevate the temperature of all fluids. The inhalational gas supplied to the patient was set at 37°C using a heated circuit.

The core BT of the patient was 37°C and his peripheral BT was 35.6°C during the surgery.

It was observed that the urine had a strong brown color [3], and at 60 minutes after anesthesia (30 minutes after the operation), blood tests showed hemoglobin at 11.0 g/dl, lactate dehydrogenase (LDH) at 494 IU/L, total bilirubin at 5.4 g/dl, and direct bilirubin at 2.1 g/dl. We decided that postoperative plasmapheresis was more appropriate than intraoperative plasmapheresis [4]. The estimated blood loss during the 600 minute surgery was 2800 ml, infused fluid HES 500 ml, and normal saline 4800 ml. Leukocyte-depleted RBC 6-units were transfused.

Therapeutic plasmapheresis was executed for 180 minutes in the intensive care unit. The patient’s blood was extracted through an arterial line and reinfused through a central venous line. Both lines were passed through fluid warmers. Therapeutic plasmapheresis was completed without any complications.

The test results were as shown in Table 1. The hemoglobin level was stable without any significant decrease; therefore, the patient was transferred to the general ward on postoperative day 5 (POD#5). During the intensive care unit (ICU) stay, the temperature taken from the arm pit was above 38°C for the first 2 days and remained at 37–38°C until the fifth day. After transfer to the general ward, RBC 1 unit was transfused on each of the following days: POD#8, POD#10, POD#13, and POD#15. The temperature taken from the arm pit remained at 38°C. The patient was discharged on POD#16 with a hemoglobin level of 8.9 g/dl, and a month after the surgery (2 weeks after discharge), the hemoglobin measured at ambulatory care was 7.4 g/dl. There were no complications afterwards.

In this case, although the cold agglutinin antibody number...
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was relatively high at 1 : 8148, the reactivity was not high due to the BT being at 36°C. The decrease in temperature during the surgery, however, might have caused the hemolytic reaction. It can be assumed that the low temperature (around 20-25°C) decreased the BT and consequently increased cold agglutinin reactivity. The high activity of cold agglutinin induced the hemolysis, the urine color change, and the high bilirubin level.

Ulvestad et al. [5] reported that hemolysis occurred after infection and trauma in a patient with chronic cold agglutinin disease. The increases in pro-inflammatory cytokines IL-1α, IL-6, TNF-α, and IFN-γ in response to trauma can cause both an increase in BT and complement-mediated hemolysis, as well as possibly trigger an exacerbation of hemolysis. The patient in this case experienced hemolysis even when a relatively high BT (above 35°C) was maintained during the surgery.

In summary, the maintenance of BT has been regarded as the most important step in the anesthetic management of cold agglutinin disease patients. However, because exposure to a relatively low temperature (25°C) could modify the cold agglutinin, hemolysis may occur even when the core BT is maintained at around 35.6°C. During surgery, the urine color must be carefully observed, and hemoglobin, direct bilirubin, and LDH must be measured to monitor for hemolysis.

References

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Table 1. Changes in Laboratory Findings

| Time           | Hb* (g/dl) | Total bilirubin (mg/dl) | Direct bilirubin (mg/dl) | LDH† (IU/L) | Cold agglutinin titer | Transfused RBC‡ (packs) |
|----------------|-----------|-------------------------|--------------------------|-------------|-----------------------|------------------------|
| Preoperative   | 9.9       | 2.9                     | 2.1                      | 1 : 8192    |                       | 3                      |
| 30 min         | 11.0      | 5.4                     | 2.1                      | 494         |                       |                        |
| 120 min        | 7.9       | 6.0                     | 387                      |             |                       |                        |
| 240 min        | 10.5      | 7.7                     | 343                      | 2           |                       |                        |
| 420 min        | 8.7       | 7.0                     | 237                      | 1           |                       |                        |
| 540 min        | 12.0      | 10.5                    | 5.6                      | 3           |                       |                        |
| 600 min        |           | 13.1                    | 6.0                      | 395         |                       |                        |
| Post-plasmapheresis | 10.7  | -                       | -                        | -           |                       | -                      |
| POD#1          | 9.6       | 8.4                     | 3.5                      | 165         | 1 : 2048              | -                      |
| POD#2          | 6.6       | 16.9                    | 10.0                     | 416         | -                     | 3                      |
| POD#3          | 9.2       | 47.1                    | 38.0                     | 466         | -                     | -                      |
| POD#4          | 8.2       | 55.1                    | 44.0                     | 493         | -                     | -                      |
| POD#5          | 9.0       | 51.4                    | 37.4                     | 472         | -                     | -                      |
| POD#6          | 8.7       | 40.2                    | 24.5                     | 476         | -                     | -                      |
| POD#7          | 8.0       | 24.5                    | 17.1                     | 576         | -                     | -                      |
| POD#8          | 6.4       | 13.9                    | 10.0                     | -           | 1 : 2048              | 1                      |
| POD#9          | 6.8       | 13.6                    | 9.2                      | -           | -                     | -                      |
| POD#10         | 6.3       | 11.3                    | 7.8                      | -           | -                     | 1                      |
| POD#11         | 7.5       | 15.0                    | 9.8                      | -           | -                     | -                      |
| POD#12         | 5.6       | 10.6                    | 6.1                      | -           | -                     | -                      |
| POD#13         | 5.2       | 8.6                     | -                        | -           | -                     | 1                      |
| POD#14         | 6.2       | 7.1                     | 4.4                      | 403         | -                     | -                      |
| POD#15         | 5.8       | 6.1                     | -                        | -           | -                     | 1                      |

*Hb: hemoglobin, †LDH: lactate dehydrogenase, ‡RBC: red blood cell, §POD: postoperative day.