Anesthesiology
72:761–764, 1990

Cholecystectomy in a Patient with Paroxysmal Nocturnal Hemoglobinuria: Anesthetic Implications and Management in the Perioperative Period

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Paroxysmal nocturnal hemoglobinuria [PNH] is a rare acquired disorder of bone marrow stem cells resulting in the production of red cells, granulocytes, and platelets with both membrane and enzyme defects. It may present as chronic intravascular hemolysis with or without a distinct nocturnal pattern or by pancytopenia, iron deficiency, or recurrent thrombotic episodes. Hemolysis occurs because of an obscure membrane defect that makes the red cell unusually susceptible to the lytic action of complement. Patients with PNH are at increased risk of hemolysis during those circumstances that increase complement activation. They are particularly at risk for hemolysis and thrombosis as a result of surgery, pregnancy, and infection.

Described here is the anesthetic management of a patient with long-standing PNH.

REPORT OF A CASE

A 48-yr-old woman presented for elective cholecystectomy as the result of persistent symptomatic cholelithiasis. The patient had had a 14-yr history of PNH initially presenting with aplastic anemia. Since then she had required red cell transfusions averaging every 6 weeks. In addition she had experienced venous thromboses of multiple extremities, and multiple episodes of bacterial infections with a recent lung abscess. She chronically maintained a marked granulocytopenia with less than 100 leukocytes. She had been receiving coumarin that was discontinued preoperatively.

Significant preoperative laboratory values included a Hb 11.6 g, a Hct 34.4, and a WBC 1200 with 100% lymphocytes. The granulocytopenia persisted throughout the hospitalization. Admitting prothrombin time was 16.2 s which decreased to within the normal range by the second postoperative day. Preoperatively, plasma-free hemoglobin was less than 50 mg/dl, confirming the absence of clinically significant intravascular hemolysis.

Because of previous episodes of thrombosis at peripheral iv sites, a right infraclavicular subclavian catheter was inserted the evening prior to surgery and, to prevent dehydration, an iv infusion was started and maintained overnight. Intraoperatively, 3300 ml of crystalloid were infused. Preoperatively the patient received vancomycin, ceftazidine, and metronidazole. In the operating room general anesthesia was induced with fentanyl, midazolam, sodium thiopental, and the patient was paralyzed with atracurium. Anesthesia was maintained with isoflurane, nitrous oxide, oxygen, and incremental doses of fentanyl and droperidol. Following trachial intubation, a foley catheter was inserted facilitating monitoring for hematuria. Two units of washed, packed red blood cells were infused at the beginning of surgery. Intraoperative hemoglobinuria was treated with 40 mg methylprednisolone with prompt clearing of the urine. The patient's postoperative course was uneventful; plasma-free hemoglobin remained low.

DISCUSSION

Paroxysmal nocturnal hemoglobinuria is a disease affecting all hematologic cell lines and probably results from the selection of a pleuipotent stem cell producing a clone of cells with abnormal membrane sensitivity to complement fixation. Any or all cell lines may be variably affected. The defect sometimes arises in the setting of bone marrow dysplasia, suggesting that an injured bone marrow or one that has lost the ability to proliferate normally, may provide the setting for the development of a clone of defective cells.[1] The association with aplastic anemia has been well documented; at least 25% of patients present with marrow aplasia.[2,3] Occasionally, pancytopenia develops later in the course of the disease.[4]

PNH is predominately a disease of young adults without sexual, racial, or familial predilection. Ultimately, the clinical manifestations of this disease appear to derive from the abnormal membrane sensitivity of erythropoietic cells. Activation of complement leads to RBC lysis and to the platelet release phenomenon resulting in thrombosis.

In its classic form, PNH is characterized by hemolytic anemia of insidious onset accompanied by nocturnal hemoglobinuria, variable degrees of jaundice, and marked hemosiderinuria with resulting iron deficiency.

Symptoms associated with hemolysis include bone and muscle aches, malaise, and fever. Intravascular thrombotic events may produce abdominal and back pain associated with mesenteric, portal, or hepatic vein thrombosis, or headache associated with cerebrovascular occlusion.[4] These thrombotic episodes have been attributed to the direct activation of platelets by complement. If aggregation follows activation thrombosis results, particularly in venous channels with slowed flows such as the hepatic vein.[5] The defects in the red cells of patients with PNH are probably a complex modification of the membrane proteins that have not yet been fully described and that

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Received from the University of Colorado Health Sciences Center, Denver, Colorado. Accepted for publication December 4, 1989.

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Key words: Blood, paroxysmal nocturnal hemoglobinuria: complement activation; hemoglobinuria; hemolysis. Complications: venous thrombosis.

result in an unusual sensitivity to the action of complement *via* the classic as well as the alternate pathways.[6] The membrane defect may be related to a recently described deficiency in a membrane regulatory protein known as "decay-accelerating factor."[7] Similar membrane defects have been described in other hematopoietic cell lines. However, not all cells in a given cell line are affected; populations of cells with different sensitivities to complement have been described. The relative proportion of each cell population determines the specific clinical pattern and may change during the course of the illness.

Infections are frequent because of leukopenia or defective leukocytes with relative unresponsiveness to chemotactic stimuli.[8] In one series of 53 deaths, five were attributed to infection, but even mild infections may constitute a serious hazard because they may precipitate an exacerbation of the hemolytic process by complement activation.[9]

PNH is associated with a striking predisposition for venous thrombosis accounting for 50% of all deaths from this disease.[10] PNH platelets have a higher affinity for the C_3 component of complement than do normal platelets. This is associated with nearly maximal release of serotonin without completion of the complement terminal sequence as is required with normal platelets. This abnormal interaction of PNH platelets with complement, known as the platelet release reaction, may explain the higher incidence of thrombosis in this disease.[11] Fatal thromboses involve the portal system or the brain. Progressive diffuse hepatic vein thrombosis (Budd-Chiari syndrome) is especially common and often runs a rapidly fatal course.

There are few references to the anesthetic management of the patient with PNH. Because of the rather rare nature of this disease, controlled studies are not feasible; available clinical information is limited to anecdotal reports. Therapeutic recommendations are based on reasonable assumptions made on the basis of the known or suspected pathophysiology of this disease. The anesthetic management of the patient with PNH mandates specific measures mitigating complement activation and decreasing red cell susceptibility to complement mediated lysis. Various anesthetic regimens have been used successfully, including regional anesthesia, spinal anesthesia, and general anesthesia, although one case report suggests that a hemolytic episode during the induction of anesthesia contributed to the patient's cardiac arrest.[11-14,†]

There exists general agreement on the basic tenets of perioperative management:

1) avoiding hypoxemia, acidosis, and dehydration;
2) the use of transfused red blood cells for prophylaxis and treatment of lytic crisis;
3) the use of corticosteroids to prevent and treat hemolysis;
4) the use of vigorous measures to prevent infection, including perioperative antibiotics, meticulous postoperative wound care, and vigorous pulmonary toilet;
5) the avoidance of drugs known to activate complement such as, acetazolamide, some radiocontrast media, magnesium compounds, and drugs formulated in Cremophor.

Induction using thiopental, ketamine, midazolam, and fentanyl have been described, as have maintenance of anesthesia with isoflurane, enflurane, and nitrous oxide.[13,14] Because of nitrous oxide's ability to reduce methionine synthetase leading to a megaloblastic bone marrow, its use in patients with bone marrow hypoplasia has been questioned.[14] Both depolarizing and nondepolarizing muscle relaxants have been used successfully.[13,14]

Patients with PNH are at great risk from complement activation associated with anaphylactoid reactions, which are reportedly common during intravascular drug administration but often go unnoticed.[15] The iv induction agents least likely to cause anaphylactoid reactions are the benzodiazepines and the opioids.[14] In this case thiopental's use was uneventful.

Most of the complement proteins have been demonstrated to respond as acute-phase reactants. Significant increases in these proteins as well as the active complex $\bar{C}_{56}$ have been demonstrated following anesthesia, surgery, and various inflammatory states. They normally decrease following induction and increase postoperatively, peaking around the fourth postoperative day.[16] This may be the explanation for the observed propensity for postoperative venous thrombosis in patients with PNH.

Transfusion of packed red cells is valuable, normal cells surviving well in patients with PNH. The protective nature of transfusion is unclear but appears related to the suppression of the production of abnormal cells by the bone marrow as well as dilution of PNH-sensitive cells by normal erythrocytes. Gockerman *et al.* demonstrated decreased preoperative hemolysis and a benign perioperative course in a 55-yr-old man undergoing revision of a bilateral aortic-iliac graft following transfusion of thawed, deglycerolized erythrocytes.[17] In this patient, transfusion resulted in a decrease from 30–35% PNH-sensitive cells to 14% without changing the complement sensitivity of the remaining abnormal cells. This suggests that although the sensitivity of cells to complement lysis is critical in determining the degree of hemolysis, the percentage of these cells in the total population is also important.

† Sugimori T, Nakanishi T, Kuze S, Higuchi A, Kanamu K: Cardiac arrest and haemolytic episode in paroxysmal nocturnal hemoglobinuria after induction of anesthesia. Hokuriku Journal of Anesthesiology 17: 83–92, 1983.

Transfusion has produced short-term remissions and has terminated lytic episodes but must be administered carefully and in the form of saline washed or frozen-thawed, deglycerolized cells.[18] Plasma contained in nonwashed preparations contain non-RBC antigens (presumably HLA antigens) capable of activating complement. The early components of complement, activated in the fluid phase around the PNH erythrocyte, can attach to the cell membrane and initiate lysis without the presence of antibody.[19]

Washed red cells were administered prophylactically to our patient. Prophylactic broad-spectrum antibiotic coverage was also administered because of this patient's repeated and recent bacterial infections. An intraoperative Foley catheter facilitated monitoring for evidence of hemolysis and allowed prompt therapeutic intervention. Corticosteroids have reportedly been effective in ameliorating hemolysis as demonstrated by this patients prompt response to methylprednisolone.[20]

Because postoperative thrombosis is particularly common, it has been suggested that anticoagulation be instituted at the first sign of thrombosis.[13] The use of heparin in PNH is controversial. Hemolytic episodes have been recorded after treatment with heparin but in others it has been used without consequences. The explanation for this may reside in the ability of a low concentration of heparin to activate the alternate pathway of complement, which in turn is inhibited at higher heparin concentrations.[21] Anticoagulation with coumadin is without similar risks and is probably the agent of choice for long-term therapy. Dextran of MW 142,000 has been shown to be of value but, because of hemorrhagic complications, antibody formation, and anaphylactic reactions, is best reserved for emergencies and then only for short periods.[22]

In this instance the patient was monitored closely with no clinical evidence of postoperative peripheral thrombophlebitis or a Budd-Chiari syndrome. Preoperative hydration helped minimize venous stasis and enhanced urine flow, protecting the kidneys from the effects of hemoglobinuria. Abnormal renal function occurs, presumably resulting from multiple renal cortical infarcts. Reductions in glomerular filtration rate are rare but virtually all patients have a defect in urinary concentrating ability.[23]

As might be expected with any hemolytic disorder pigment gallstones occur.[24] Peptic ulceration appears to be prevalent and mesenteric thrombosis has been reported.[25] It is therefore reasonable to expect these patients to require major surgical procedures. While surgery itself may initiate hemolysis, indicated major surgery should not be withheld. Proper preparation of the patient with adequate hydration, the use of washed red cells, diligent intraoperative monitoring, and a stress-free anesthetic regimen will minimize the risks to the patient. Because of the highly variable presentations of this disease, management must be individualized.

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Anesthesiology
72:764–766, 1990

Transient Anterior Spinal Cord Syndrome with Continuous Postoperative Epidural Analgesia

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An unusual case of an anterior spinal artery syndrome involving a single lower limb is described. The differential diagnosis, management, and possible causes are described.

CASE REPORT

A 59-yr-old, 157-cm tall, 45-kg woman underwent an ileal loop urinary diversion because of a 19-yr history of urinary incontinence. The cause of incontinence was unknown, there were no abnormal neurological signs, and the voiding urethrogram was normal.

There had been no problem with general anesthetics for two bladder suspensions, cesarean section, or total abdominal hysterectomy for fibroids. Spinal anesthesia for a second cesarean section was also uneventful.

Laboratory tests of renal function and coagulation were normal, as were the chest x-ray and electrocardiogram.

In the operating room, an epidural catheter was inserted *via* the L2-3 interspace using a 17-G Touhy needle with the patient in the lateral position. No evidence of intrathecal or iv injection was detected following a 3-ml test dose of 1.5% lidocaine with 1 in 200,000 epinephrine. General anesthesia was induced with sodium thiopental (300 mg) and succinylcholine (80 mg), and following tracheal intubation, anesthesia was maintained with nitrous oxide (60%), oxygen, and isoflurane (0.5–1% delivered concentration). Controlled ventilation (normocapnia) was facilitated by pancuronium. Analgesia was provided by 5-ml increments of 0.5% plain bupivacaine to a total of 25 ml during the anesthetic time of 5.25 h. Preoperative blood pressure was 130/80 mmHg and was approximately 100 mmHg systolic intraoperatively, decreasing three times to 90 mmHg, lasting a total of 10 min. Oxyhemoglobin saturation throughout remained at or above 98%. Surgery proceeded uneventfully, blood loss was estimated to be 500 ml, and she received 3,500 ml of lactated Ringer's solution. Tracheal extubation occurred following reversal of muscle relaxation. Forty-five minutes after surgery, review by the staff anesthesiologist revealed that she was moving all her limbs and verbalizing coherently. Fentanyl 100 μg in 10 ml of preservative-free normal saline was administered *via* the epidural catheter. Following transfer to the ward, continuous epidural analgesia was maintained with an infusion of fentanyl 10 μg/ml in preservative-free normal saline at a rate of 40 μg/h. At 2 h postoperatively she was reviewed by the anesthesiology resident from the Acute Pain Service. She was pain free, oriented, moving all limbs, and had regained sensation in her legs.

At 2 A.M., approximately 12 h after surgery, the patient awoke and complained to the nurse of numbness and weakness of the left leg. She was immediately reviewed neurologically and was lucid, oriented, and denied any pain. There was sensory loss to touch, pinprick, and cold involving the entire left leg from the inguinal ligament distally. Tone and power of the left leg were markedly reduced with only some very weak knee extension possible. The other limb was normal and anal tone was moderate. The epidural site appeared normal and nothing could be aspirated through the catheter.

A provisional diagnosis was made of epidural nerve root compression, probably due to an epidural hematoma. The epidural infusion was discontinued and an emergency neurosurgical consultation was obtained. The physical signs were confirmed and an anterior-posterior x-ray of the lumbar spine and computerized tomography were performed (figs. 1 and 2). These showed a scoliosis, convex to the right caused by an L_4 hemivertebra (two right pedicles and foramina and one left pedicle and foramen). Intravenous contrast enhancement failed to show the epidural catheter or a space-occupying lesion, and therefore, a few ml of contrast medium were injected through the catheter. It was seen to enter the spinal canal just above the lamina of L_3 and coursed along the left anterolateral aspect of the canal (fig. 2) in a cephaled direction. Its tip entered a left-sided intervertebral foramen, probably T_{12}-L_1. No hematoma or space-occupying lesion were demonstrated; in fact, there was ample space around the lumbar nerve roots and there was free flow of contrast out into the intervertebral spaces (fig. 2).

With the exclusion of epidural nerve root or spinal cord compression, the patient was transferred back to the ward, the catheter was removed intact, and her neurological state reassessed. At this examination, approximately 15 h after surgery, position sense was tested for the first time and found to be present at the great toe and the ankle. Unfortunately, vibration sense was not tested. The physical signs were, therefore, compatible with a lesion in the distribution of the anterior spinal artery on the ipsilateral side to the monoparesis.

A neurologic consultation was obtained, the diagnosis of a probable

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Received from the Department of Anesthesiology, The Oregon Health Sciences University, Portland, Oregon. Accepted for publication December 4, 1989.

Key words: Analgesics, epidural: fentanyl. Anesthetic technique: epidural. spinal cord: complication.

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