Fatal hemolytic transfusion reaction due to anti-Ku in a $K_{\text{null}}$ patient

M. Lin, C.L. Wang, F.S. Chen, and L.H. Ho

A fatal transfusion reaction due to anti-Ku in a $K_{\text{null}}$ ($K_0$) patient is reported. The patient was transfused with 34 units of incompatible RBCs during 44 days of hospitalization. Apart from the first transfusion, all subsequent transfusions failed to raise the patient's Hb. No serum antibody was identified until he was transferred to another hospital for dialysis. A compatibility test demonstrated a weak antibody and autocontrol reacting at room temperature by a manual polybrene method. The antibody was considered to be a "cold agglutinin." A blood sample was sent to a reference laboratory where the patient was found to be $K_{\text{null}}$ and the antibody was identified as anti-Ku. *Immunohematology* 2003;19:19–21.

**Key Words:** anti-Ku, $K_{\text{null}}$ phenotype, hemolytic transfusion reaction

A hemolytic transfusion reaction and hemolytic disease of the newborn due to anti-Ku were initially described by Chown et al.1 This first case of $K_{\text{null}}$ was in a person of Polish ancestry. Among other reported cases of $K_{\text{null}}$ persons, one was Japanese and the other 13 were Caucasian.2 The first $K_{\text{null}}$ phenotype in a Northern Han Chinese person was found during phenotyping of 50 group O blood donors in the Beijing Blood Center. A family study identified two $K_{\text{null}}$ siblings. Anti-Ku was not detected in their serum. The parents were not consanguineous. Our patient was a military veteran from the Yunnan province in southern China, which has more than 25 ethnic minorities. He had an unusual last name, suggesting that he could be of a minority group. Additional family history was not available.

**Case Report**

A 79-year-old native of Yunnan, China, with a history of nephrolithotomy was admitted to a remote military hospital on 4/11/00 with mild impaired renal function and a Hb of 7.7 g/dL (Table 1). His history of previous blood transfusion was not available. No atypical antibody was identified and IATs were not performed. Three units of RBCs were transfused without adverse reaction. The Hb showed the expected increase to 10.3 g/dL considering his weight of 50 kg. Left nephrectomy due to perirenal abscess was performed on 5/4/00 and four units of RBCs were transfused. They were associated with chills, but no adverse reaction was noted when two more units of RBCs were transfused the next day. The Hb was 9.9 g/dL on 5/6/00 (Table 1). After transfusion of a further three units of RBCs on 5/9/00, the patient was found to be apprehensive and anxious. During the last 16 days of his life, the patient developed renal failure, respiratory failure, anemia, and jaundice and was treated for sepsis and uremia. The patient was also found to have chronic liver disease. Twenty-five units of RBCs were transfused during this 16-day period but the expected increase in Hb was not observed. He was transferred to another hospital for hemodialysis on 5/17/00. There, for the first time, his serum demonstrated a "cold agglutinin." His antibody was later identified as anti-Ku by a reference laboratory. He expired on 5/24/00. The clinical course is shown in Table 1.

**Materials and Methods**

RBC phenotyping was performed by using commercial antisera (Gamma Biologicals, Inc., Houston, TX, and DiaMed SA, Cressier sur Morat, Switzerland) except for anti-Jsa, which was a gift of Ortho-Clinical Diagnostics, Raritan, New Jersey. Gamma-clone anti-IgG and Bioclone anti-C3d (Ortho-Clinical Diagnostics) were used as anti-human globulin (AHG) reagents.

The manual polybrene method (a tube test) was performed at room temperature by using reagents prepared in house according to the method of Lalezari and Jiang,3 and Fisher,4 but without the supplementary AHG phase. Polybrene (hexadimethrine bromide) was purchased from Sigma Chemical Co., St. Louis, Missouri.
Results

During compatibility testing on 5/17/00, a weak antibody of broad specificity, reacting at room temperature and by a manual polybrene tube method (1+), was noted. Since the autocontrol was also positive, although weaker, the antibody was considered to be a cold agglutinin. Three days before the patient died, a blood sample was sent to the Immunohematology Reference Laboratory, Mackay Memorial Hospital. There, the patient was found to be Knull, and the broad-reacting antibody was identified as anti-Ku. The patient's anti-Ku reacted 1+ by the manual polybrene tube method and was slightly stronger (2+) by the LISS-IAT. The patient's RBCs had a positive DAT (anti-IgG 1+w; anti-C3d ±), and his serum reacted with all RBCs tested, including panel cells (DiaPanel); 30 group O Taiwanese donor RBCs; and other rare cells, including Di(a+ b–) and Vel– RBCs, but not with Knull RBCs. The patient's RBCs typed as group O, D+, C+, E–, c+, e+, K-, k-, Kp(a– b–), Js(a– b–), Fy(a+b–), and Jk(a+b+). His RBCs failed to react with two examples of anti-Ku obtained from the Serum, Cells, and Rare Fluids International Exchange Group (SCARF). These examples were obtained from two group A, Ko individuals, one from Germany and the other from the United States. Molecular studies revealed a G to C substitution at the splice donor site (5′ splice site) of intron 3 of the KEL gene to be present in this patient. This substitution abolishes expression of the Kell blood group system antigens. Laboratory test results are detailed in Table 1.

Discussion

The standard pretransfusion test in Taiwan is the manual polybrene tube method without an AHG phase, because the frequency of K in Taiwan is 0 percent and anti-K has not been reported. No individuals of the Knull phenotype have been identified among “Taiwanese” (the descendants of early settlers from the southeast coast of China) or among Taiwan’s indigenous tribes after phenotyping more than 3000 individuals. Therefore, it is not surprising that this case is probably the first alloantibody of the Kell blood group system to be found in Taiwan. It is not possible to determine when anti-Ku first occurred in this man, because his history of previous blood transfusions is not available and because the antibody in his serum was not detected until 5/17/00. Because a reasonable increase in Hb was observed after his transfusion on 4/11/00, the alloantibody could have been induced during this admission, although the possibility of an anamnestic response due to preexisting anti-Ku cannot be excluded. The “cold agglutinin” was reported on 5/17/00, after the patient had been transfused with 30 units of RBCs. A diagnosis of a hemolytic transfusion reaction was based on the rapid impairment in renal function (which was also compromised by a prior nephrectomy, urinary tract infection, and sepsis); direct and total bilirubin levels of 9.8 mg/dL and 13.8 mg/dL, respectively; and, subsequent to the initial blood transfusion, the failure to observe the expected increase in Hb.

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<td>Hb g/dL</td>
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Clinical notes:

4/11 Admission
5/4 Left nephrectomy for perirenal abscess
5/9 Acute gastritis with hemorrhage
5/12 Lung edema, jaundice, positive urine and blood cultures, hypotension, fever
5/17 Hemodialysis for uremia, acute respiratory failure
5/21 Anti-Ku identified
5/24 Coma and death
Fatal transfusion reaction due to anti-Ku

Acknowledgment
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References

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BOOK REVIEW

Evidence-Based Practice of Transfusion Medicine.

Occasionally one experiences the awful awareness of gaps in one’s knowledge or training that make some subjects too intimidating to tackle. Agreeing to review the book Evidence-Based Practice of Transfusion Medicine meant I had to tackle one of those areas.

To quote the author, “Evidence-based medicine requires the user to select the best of relevant studies and while noting their strengths and weakness, extract the clinical message in order to solve specific patient problems.” The intent of this book is to present the rationale of clinical research methods to those readers who may well understand laboratory research methods but are less able to undertake a critical analysis of clinical research reports.

The author appears well aware that blood bankers often lack training in this area. He begins the book with three introductory chapters on basic concepts such as measurement of disease occurrence and association, then moves on to research designs, role of chance and bias, statistical hypothesis testing, and the meaning of sensitivity and specificity.

One of the strengths of this book is its single author who, in each chapter, discusses the research behind such controversial topics as the risk of transfusion-transmitted viral infections, current issues in transfusion-transmitted hepatitis C, the potential for transfusion transmission of Creutzfeldt-Jakob disease (CJD) and variant CJD, cost-effectiveness of autologous donation, trends in the blood supply, and the confusing issue of immune modulation as it relates to universal leuko-reduction. Each chapter reviews these issues logically, notes what studies should be done to provide a scientifically based policy decision, and provides extensive references.

One of the most challenging but rewarding chapters is on meta-analysis in transfusion medicine. As the author points out, such analysis will be used to formulate policy guidelines and if used properly can “use statistics to clarify not obfuscate,” a quote from a journal article by Goodman. Have you ever met a meta-analysis you didn’t like? Ann Intern Med 1991;114:244-6.

This book should be helpful to many and should be used by educators to improve training in statistical analysis of clinical research. If it is updated periodically it will be a most useful source of in-depth reviews on controversial topics.

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Carrollton, KY 41008

Manuscripts: The editorial staff of Immunohematology welcomes manuscripts pertaining to blood group serology and education for consideration for publication. We are especially interested in case reports, papers on platelet and white cell serology, scientific articles covering original investigations, and papers on the use of computers in the blood bank. Deadlines for receipt of manuscripts for the March, June, September, and December issues are the first weeks in November, February, May, and August, respectively. Instructions for scientific articles and case reports can be obtained by phoning or faxing a request to Mary H. McGinniss, Managing Editor, Immunohematology, at (301) 299-7443, or see “Instructions for Authors” in every issue of Immunohematology or on the Web. Include fax and phone numbers and e-mail address with your manuscript.
Monoclonal antibodies available. The New York Blood Center has developed murine monoclonal antibodies that are useful for donor screening and for typing red cells with a positive DAT. Anti-Rh17 is a direct agglutinating monoclonal antibody. Anti-Fy$a$, anti-K, anti-J$s^b$, and anti-Kp$^a$ are indirect agglutinating antibodies that require anti-mouse IgG for detection. These antibodies are available in limited quantities at no charge to anyone who requests them. Contact: Marion Reid, New York Blood Center, 310 E. 67th Street, New York, NY 10021; e-mail: mreid@nybc.org

Workshop on Blood Group Genotyping. The ISBT/ICSH Expert Panel in Molecular Biology has recommended that a workshop be held on blood group genotyping by molecular techniques. The result of the meeting would culminate in a report at the ISBT Congress in 2004 in Edinburgh. It was decided that only laboratories that provide a reference service in blood group genotyping would be included in the workshop. One of the aims of the workshop would be to establish an external quality assurance plan. If you have any suggestions as to how the workshop should be organized, we would be grateful for your opinions. If you are interested in taking part in such a workshop, please contact Geoff Daniels (geoff.daniels@nbs.nhs.uk). Offer presented by Geoff Daniels, Martin L. Olsson, and Ellen van der Schoot.

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Where: Mayo Civic Center, Rochester, MN

This conference promotes who we are as laboratory professionals. It is a key resource for networking with other professionals from across the state and region. These 3 days will provide attendees with opportunities for continuing education in areas of personal and professional growth. Explore the newest equipment and testing available in the field while visiting the many vendor displays. Social events are planned for your enjoyment. A silent auction will be held with all proceeds benefitting the Children's Miracle Network. The career fair has been expanded to 2 days. This conference is sponsored by: American Association of Clinical Chemistry—Midwest section, Association of Genetic Technologists, American Society for Clinical Laboratory Science—Minnesota, American Society for Clinical Pathology—Associate Member Section, Clinical Laboratory Management Association—Minnesota Chapter, Minnesota Association of Blood Banks, Minnesota Interlaboratory Microbiology Association, and Minnesota State Society of American Technologists.

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Contact: Rose Currie at currie.rose@mayo.edu

MS Program. A university-based regional blood center and transfusion service is accepting application for fall quarter 2003 for two, 2-year Master's programs. The Blood Transfusion Medicine program emphasizes all aspects of transfusion medicine, including cellular therapies, transplantation immunology, immunohematology, blood center and transfusion service operations, quality assurance, component therapy, and independent research. Students simultaneously fulfill the requirements for SBB certification. The Cellular Therapies program emphasizes the biology and therapeutic use of hematopoietic stem cells and other somatic cell therapies. The program includes significant hands-on laboratory experience in selection and genetic manipulation of stem cells and in the development of novel cell therapy treatment protocols. Application deadline: April 1, 2003. Contact: Cathy Beiting, MS, MT(ASCP)SBB, Hoxworth Blood Center, University of Cincinnati Medical Center, 3130 Highland Avenue, PO Box 670055, Cincinnati, OH 45267-055. Phone: (513) 558-1275; e-mail: catherinebeiting@uc.edu