(Phosphoenolpyruvate), PYR (Pyruvate), LAC (Lactate), 6PG (6-phosphogluconate), PRPP (Phosphoribosyl pyrophosphate), R5P/Ru5P (Ribose 5-phosphate / Ribulose 5-phosphate), Xu5P (Xylulose 5-phosphate) and S7P (Sedoheptulose 7-phosphate) were analyzed by MRM based LC-MS/MS method. Data are presented as mean ± SD. (B) Enzymatic activities of glycolysis enzymes were assayed with RBC lysate prepared from 8-week-old WT and Nmnat3$^{gt/gt}$ mice (n = 4 for each group). PFK (phosphofructokinase), ALD (aldolase), PK (pyruvate kinase), HK (hexokinase), GPI (glucose 6-phosphate isomerase), TPI (triose phosphate isomerase), PGK (phosphoglycerate kinase), ENOL (enolase) and LDH (lactate dehydrogenase) were measured by the methods recommended by International Committee for Standardization in Hematology. (C) Immunoblot analysis of PFK and GAPDH in mature erythrocytes from WT and Nmnat3$^{gt/gt}$ mice. β-Actin was used as loading control. Proteins were extracted from three mice for each group. (D) Enzymatic activities of pentose phosphate pathway enzymes (G6PD; glucose 6-phosphate dehydrogenase, 6PGD; 6-phosphogluconolacton dehydrogenase) were assayed with RBC lysate prepared from 8-week-old WT and Nmnat3$^{gt/gt}$ mice (n = 4 for each group). (E) Enzymatic activities of AK (adenylate kinase) and ADA (adenosine deaminase) were assayed with RBC lysate prepared from 8-week-old WT and Nmnat3$^{gt/gt}$ mice (n = 4 for each group). (F) Measurement of Acetyl-CoA level in RBC prepared from WT and Nmnat3$^{gt/gt}$ mice (n = 4 for each group). (G) Acetylation status of erythrocytes protein. RBC lysates were separated by SDS-PAGE and subjected to immuno blotting with acetyl-lysine specific antibodies (Abcam and Cell Signaling). Proteins were extracted from three different mice for each group.

Figure 7. Glucose flow is shifted to pentose phosphate pathway and reversed from GAP to F1,6BP in Nmnat3$^{gt/gt}$ erythrocytes. (A) Primary cultured erythrocytes prepared from WT and Nmnat3$^{gt/gt}$ mice were cultivated in the medium containing [U-13C]-glucose. 13C-labeled metabolites were monitored by MRM based LC-MS/MS method. Samples were harvested at the time point of 0, 30, 60, 90 and 120 min. Data are presented as mean ± SD (n = 4 for each group). (B) Schema of carbon flow by [1,2-13C] glucose tracer analysis. White and red circles are 12C and 13C, respectively. (C and D) Primary cultured erythrocytes prepared from WT and Nmnat3$^{gt/gt}$ mice were cultivated in the medium containing [1,2-13C]-glucose. Different isotopomers of 13C-labeled F1,6BP (C) and R5P/Ru5P (D) were monitored by MRM based LC-MS/MS method. Samples were harvested at the time point of 0, 30, 60, 90 and 120 min. Data are presented as mean ± SD (n = 4 for each group). (E) Measurement of ATP level in whole blood collected from WT and Nmnat3$^{gt/gt}$ mice (n = 4 for each group). Data are presented as mean ± SD.

Figure 8. Schematic of the hemolytic anemia in Nmnat3$^{gt/gt}$ mice. Nmnat3 is the dominant Nmnat among the three isoforms in mature erythrocytes, and its deficiency leads to a drastic depletion of the NAD pool. A lowered NAD level inhibits glycolysis at GAPDH and reverse the glycolytic flow between F1,6BP and GAP. Impaired ATP synthesis in Nmnat3$^{gt/gt}$ erythrocytes leads to the dysfunction of Na^+-K^+-ATPase and a resulting spiked shaped erythrocytes, which are preferentially trapped and destroyed by the reticuloendothelial system of the spleen. Thus, Nmnat3 deficiency in mice caused splenomegaly and hemolytic anemia.

Table 1

Genotyping primers for Nmnat3$^{gt/gt}$ mice	
Primer #1	TCTTCTGGGGTCGCAGTTAT
Primer #2	CCTTCTTTCTGGTCTTTCTCTGTGCAA
Primer #3	TGCCACCTGACGTCTAAGAA
Primer #4	GACAGTGCAGCGATGTCCTA

qPCR primers for mouse Nmnat3	
Nmnat3-Ex1	FWD: GTGTCCACGAAGCCTTGAGT
	REV: CAGCCATCTGACTCTGTCGT
Nmnat3-Ex2-3	FWD: CACCAAACAGGAAGGTACCA
	REV: AAGCCACCAGGTCTTTCTTC
Nmnat3-Ex5	FWD: CAGGGTTCCCAATATCCTGA
	REV: TCAAACAAGCAGGCAGTCAT
B2m (Beta-2-microglobulin)	FWD: TTCTGGTGCCTTGTCTCACTGA
	REV: CAGTATGTTCGGCTTCCCATTC
Rpl13a (ribosomal protein L13a)	FWD: AGCGCCTCAAGGTGTTGGA
	REV: GAGTGGCTGTCACTGCCTGGTA

Table 2

Peripheral blood cell count

	WT	Nmnat3$^{gt/gt}$	*p* value
RBC (×10^4/μL)	730±12.2	483±11.8	p<0.0001
Hb (g/dL)	11.2±0.299	7.70±0.141	p<0.0001
Ht (%)	37.0±0.825	25.4±0.480	p<0.0001
MCV (fL)	50.7±0.804	52.6±0.545	p<0.05
MCH (pg)	15.4±0.258	16.0±0.206	p<0.05
MCHC (%)	30.4±0.311	30.4±0.386	n.s.
WBC (×10^2/μL)	24.3±5.44	16.8±5.68	n.s.
Neu (%)	17.3±3.40	13.0±3.56	n.s.
Lym (%)	78.0±5.29	84.5±3.79	n.s.
Ba (%)	0.00±0.00	0.00±0.00	n.s.
Eo (%)	2.00±1.83	1.00±0.82	n.s.
Mo (%)	2.75±0.96	1.50±1.29	n.s.
PLT (×10^4/μL)	87.3±7.83	76.2±2.62	n.s.
Reticulocyte (‰)	36.0±1.41	236±10.2	p<0.0001

Figure 1

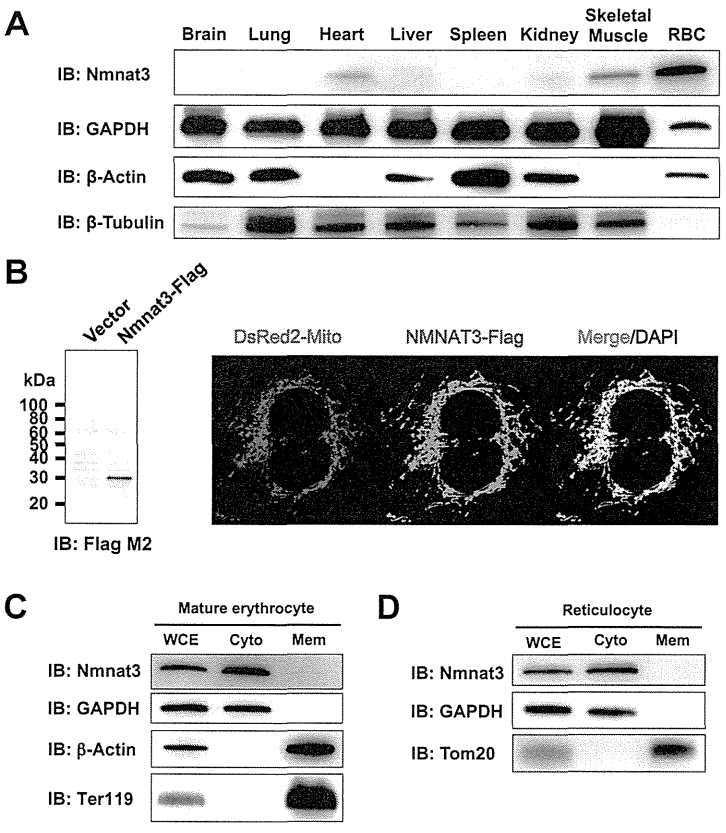
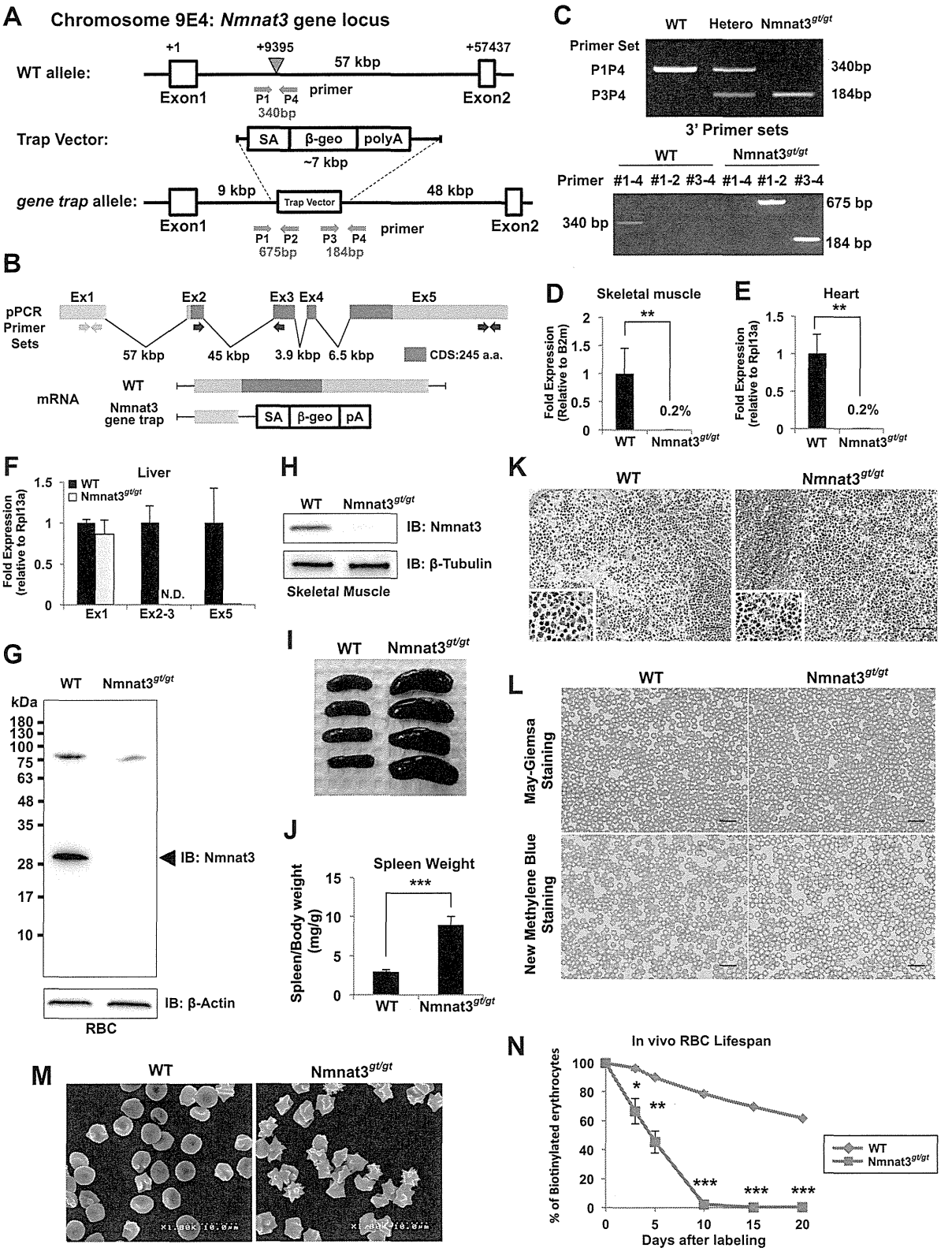


Figure 2



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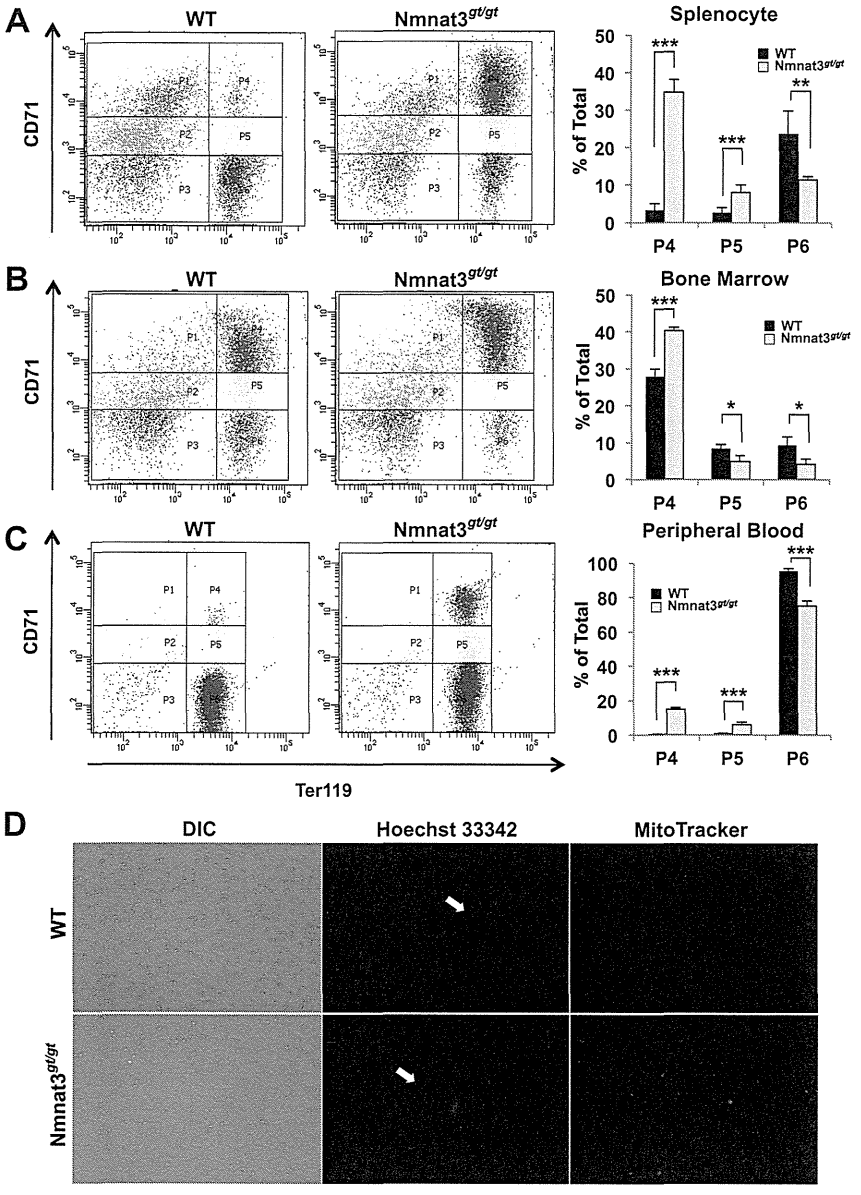
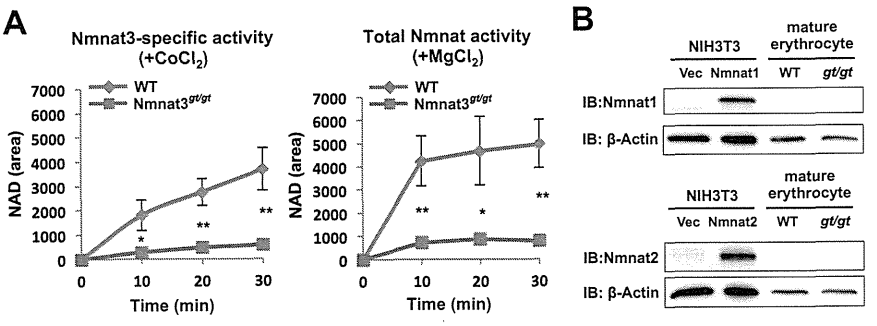


Figure 4



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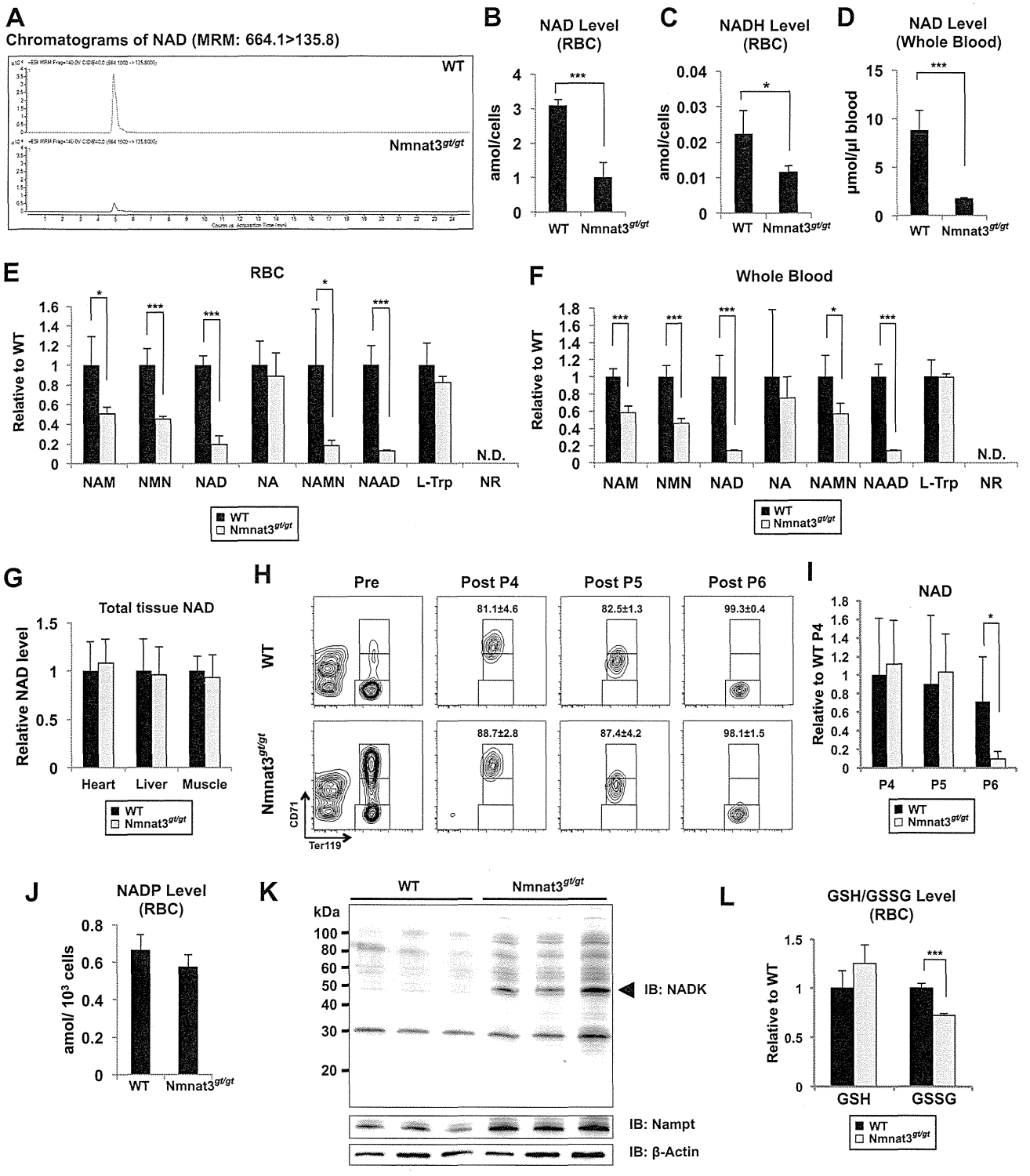

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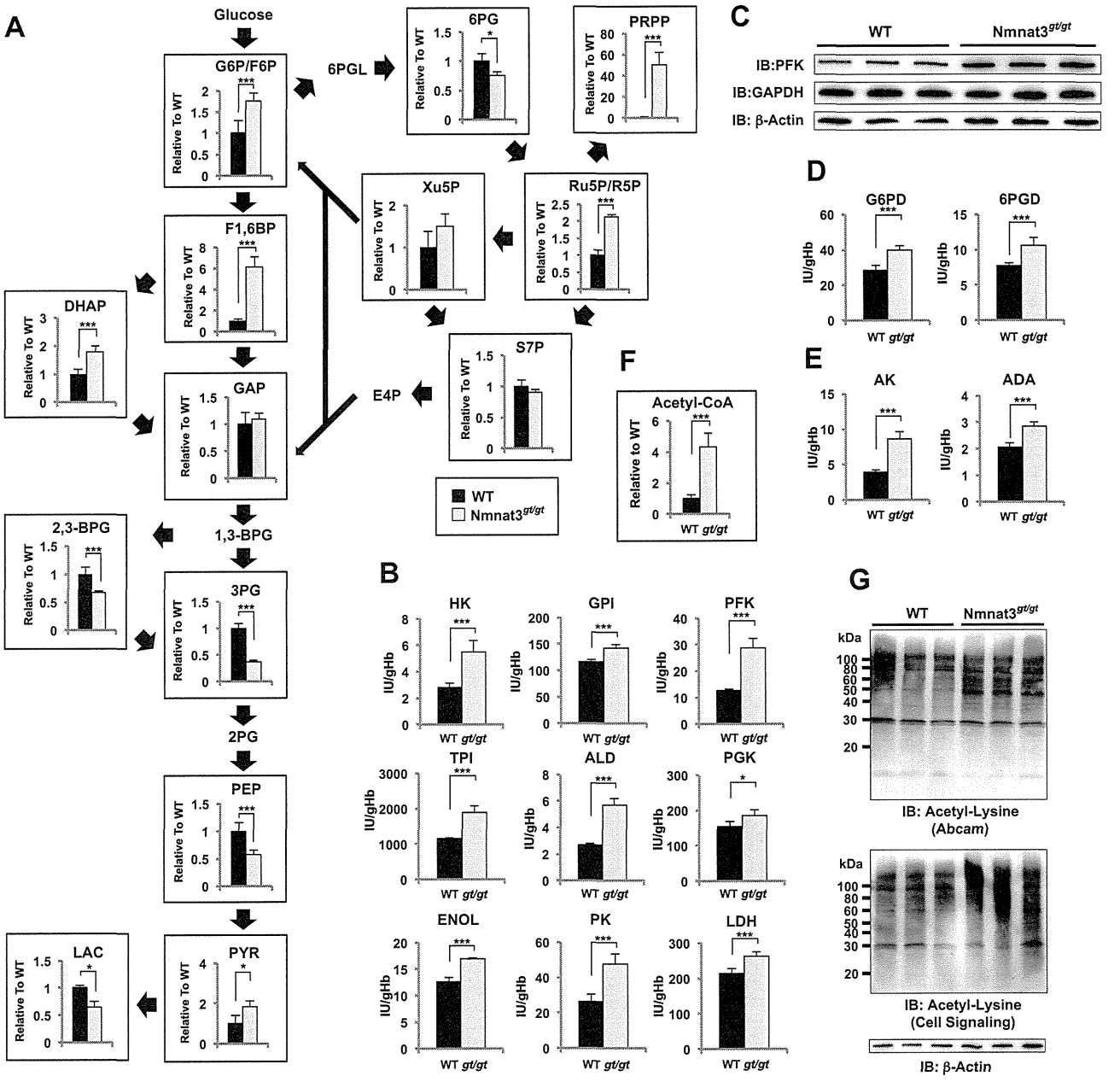


Figure 7

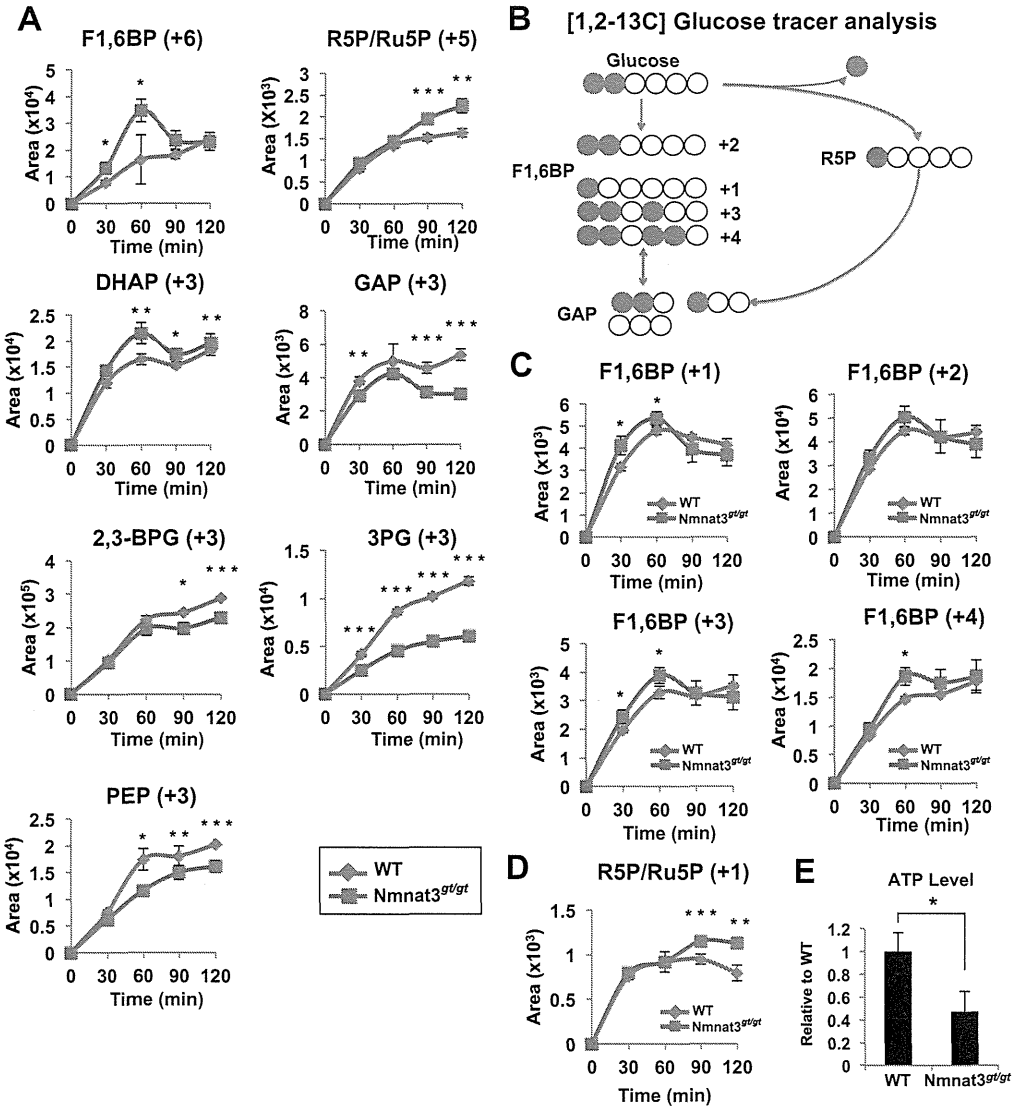
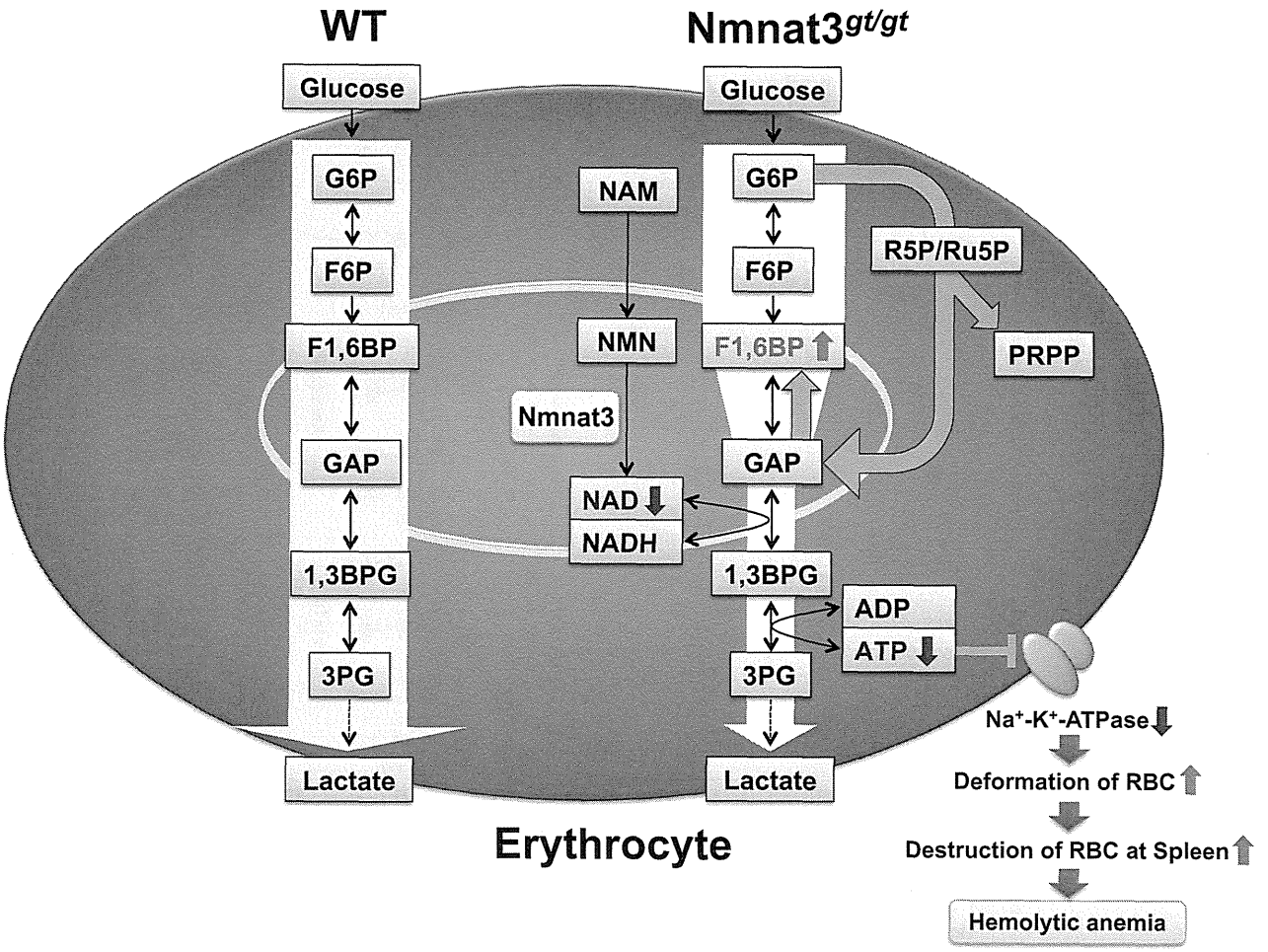


Figure 8


WT
Nmnat3gt/gt
Glucose
Glucose
G6P
F6P
F1,6BP
GAP
1,3BPG
3PG
Lactate
NAM
NMN
Nmnat3
NAD
NADH
G6P
F6P
F1,6BP
R5P/Ru5P
PRPP
GAP
1,3BPG
ADP
ATP
3PG
Lactate
Erythrocyte
Na+-K+-ATPase
Deformation of RBC
Destruction of RBC at Spleen
Hemolytic anemia

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CASE REPORT Open Access

Human parvovirus B19-induced aplastic crisis in an adult patient with hereditary spherocytosis: a case report and review of the literature

Yujin Kobayashi[1,2*], Yoshihiro Hatta[1], Yusaku Ishiwatari[2], Hitoshi Kanno[3] and Masami Takei[1]

Abstract

Background: Although there are several case reports of human parvovirus B19 infection in patients with hereditary spherocytosis, no systematic reviews of adult patients with hereditary spherocytosis with human parvovirus B19 infection have been published as clinical case reports. In this study, we report a case of aplastic crisis due to human parvovirus B19 infection in an adult patient with hereditary spherocytosis.

Case presentation: A 33-year-old woman with hereditary spherocytosis and gallstones was admitted because of rapid progress in marked anemia and fever. Although empiric antibiotic therapy was prescribed, her clinical symptoms and liver function test worsened. Because the anti-human parvovirus B19 antibody and deoxyribonucleic acid levels assessed by polymerase chain reaction were positive, the patient was diagnosed with aplastic crisis due to the human parvovirus B19 infection.

Conclusion: We collected and reviewed several case reports of patients with hereditary spherocytosis aged > 18 years with human parvovirus B19 infection between 1984 and 2010. A total of 19 reports with 22 cases [median age, 28 years (range, 18–43 range); male: female ratio, 6:16], including the present case were identified. The male-to-female ratio of 6:16 implied that younger females were predominantly affected. Although fever and abdominal symptoms were common initial symptoms, liver dysfunction or skin eruptions were less commonly documented. Anti-human parvovirus B19 antibody or deoxyribonucleic acid levels assessed by polymerase chain reaction was commonly used to diagnose human parvovirus B19 infection and may be useful to distinguish human parvovirus B19 infection from other abdominal infection in patients with hereditary spherocytosis.

Keywords: Hereditary spherocytosis, Human parvovirus B19, Aplastic crisis

Background

Human parvovirus (HPV)-B19 infection can cause aplastic crisis in a patient with hereditary spherocytosis (HS) associated with chronic hemolysis [1]. Although there are several case reports of HPV-B19 infection in patients with HS, particularly in children, no reports have reviewed this infection in a series of adult patients. In this study, we report a case of HPV-B19 infection-induced aplastic crisis in an adult patient. In addition to this case, we reviewed several adult patients with HPV-B19 infection and HS.

Case presentation

A 33-year-old woman was transferred to our hospital because of fever, general fatigue, nausea, and progressive anemia. The patient's condition was normal until 1 week before admission, when she experienced flu-like symptoms such as fever, general fatigue, and abdominal discomfort. The patient was diagnosed with HS at the age of 6 in another hospital by the presence of hemolytic anemia, spherocytosis, increased fragility of spherocytes by osmotic fragility testing, and the absence of antibodies by direct or indirect Coombs test. Asymptomatic gallstones were diagnosed at the age of 19. The patient had undergone her annual blood test examination, and her hemoglobin concentration was maintained at approximately 10–12 g/dl. The patient was not under routine medications. Neither her parents nor her siblings

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had a history of HS. On admission, vital signs were as follows: blood pressure, 108/56 mmHg; pulse rate, 100 beats/min; body temperature, 39.0°C; and respiration rate, 12 breaths/min. While breathing ambient air, the patient's oxygen saturation rate was 100%. On examination, she was alert, the skin and conjunctivae were pale, and the enlarged spleen was palpable from the costal margin. No skin rash or lymphadenopathy was observed; other physical findings were normal. The results of laboratory tests were as follows: white blood cell count was 2.97×10^9/l (granulocytes, 35%; lymphocytes, 44%; atypical lymphocytes, 9%; and monocytes, 12%), red blood cell count was 1.68×10^{12}/l; hemoglobin concentration was 5.4 g/dl; hematocrit was 14.4%; mean corpuscular volume was 86 fl; mean corpuscular hemoglobin was 32.1 pg; mean corpuscular hemoglobin concentration was 37.5%; and platelet count was 84×10^9/l. Reticulocytes decreased to 0%. Spherocytosis was present on the peripheral blood smear. Liver function tests revealed levels of aspartate transaminase (AST) of 39 IU/l, alanine aminotransferase (ALT) of 31 IU/l, lactate dehydrogenase (LDH) of 342 IU/l, alkaline phosphatase (ALP) of 144 IU/l, γ-glutamyl transpeptidase (γ-GT) of 23 IU/l, total bilirubin of 2.9 mg/dl, and direct bilirubin of 1.0 mg/dl. Hepatitis B virus surface antigen and anti-hepatitis C virus antibody were negative. Haptoglobin concentration decreased to 2 mg/dl, and the direct antiglobulin test was negative. Phosphatidylinositol glycan deficient clone was ruled out by flow cytometry. In addition to the past history, the presence of spherocytes on the peripheral blood smear, and the presence of gallstones, the definite diagnosis of HS was made with lower fluorescence of eosin-5-maleimide (EMA)-stained red blood cells due to the decreased amount of target proteins by a flow cytometry-based test (EMA binding test) [2] and shortened the acidified glycerol lysis test (AGLT) value [3] after admission. Because of high fever, history of gallstones, and the presence of pancytopenia, empiric administration of antibiotics was initiated for possible abdominal infection. The patient received two units of packed red blood cell and showed marked clinical improvement. On the 7th hospital day, fever relapsed and gastrointestinal symptoms (abdominal discomfort and nausea) worsened. Liver function tests showed levels of AST as 492 IU/l, ALT as 320 IU/l, LDH as 517 IU/l, ALP as 351 IU/l, γ-GT as 166 IU/l, total bilirubin as 2.1 mg/dl, and direct bilirubin as 1.0 mg/dl. Computed tomography of the abdomen showed splenomegaly and gallstones, without hepatobiliary tract infection. Magnetic resonance cholangiography revealed no evidence of choledocholithiasis; blood cultures were negative. The results of anti-HPV immunoglobulin M (IgM) and immunoglobulin G (IgG) measured at admission were both positive, and HPV-B19 deoxyribonucleic acid (DNA) increased to 10^5 copy/ml by quantitative real-time polymerase chain reaction (PCR) using the patient's peripheral blood. Thus, HPV-B19-induced aplastic crisis was diagnosed. Because of rapid recovery of hematopoiesis and clear evidence of HPV infection, bone marrow aspiration was not performed during admission. Liver function tests returned to normal without treatment. On the 14th hospital day, the patient was discharged without any symptoms, and the hemoglobin concentration elevated to 8.9 g/dl (Figure 1).

We systematically reviewed the case reports of HPV-B19 infection that occurred in adult patients with HS and conducted a literature search using the "Pubmed" search engine. The following terms "hereditary spherocytosis" and "parvovirus B19" were used to identify the appropriate peer-reviewed, English-language papers. We collected cases of adults, defined as patients over 18 years of age, and excluded pediatric cases. In addition to the present case, we reviewed all these cases, collected clinical information described in these articles, if written, and discussed the outcome. Between 1984 and 2010, a total of 19 reports with 22 cases, including the present case were identified [4-21]. Patients' characteristics, including those of the present case, are summarized in Table 1. Family history of HS was detected in 13 cases. Fever and liver dysfunction was documented in 18 and 4 cases, respectively. Skin manifestation was documented in only 2 cases. HPV-B19 infection was diagnosed through detection of anti-HPV B19 antibody in 12 cases, HPV-B19 DNA using PCR in 1 case, both antibody and PCR in 7 cases, and others in 2 cases.

Discussion

In this study, we presented a case of HPV-B19-induced aplastic crisis in an adult patient with HS, and we performed a review of clinical features of previously published cases. The results of our review showed that all patients were young, aged 18–43 years. Retrospective studies of immunocompetent subjects infected with parvovirus B19 showed that affected patients were relatively young; in one

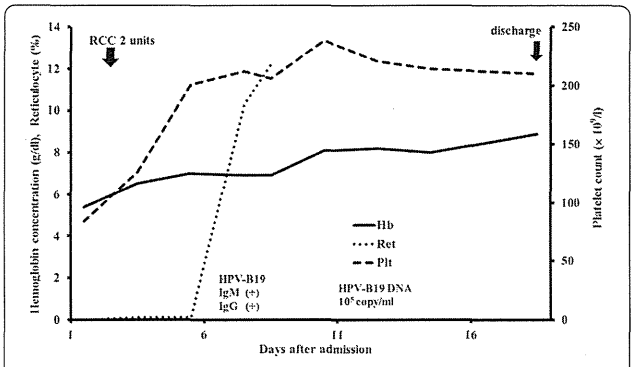

Figure 1 Clinical course of the patient. Abbreviations; RCC- Red Cell Concentrates, HPV-human parvovirus, Hb- hemoglobin, Ret- reticulocyte, Plt- platelet.

Table 1 Clinical characteristics of 22 cases with human parvovirus B19 (HPV-B19) infection in adult patients with hereditary spherocytosis

Reference	Age	Gender	Initial symptom	Family history of HS	Fever	Splenomegaly	Liver test abnormality	Skin manifestation	Gallstone	Detection of HPV-B19
[4]	33	Female	Fever, abdominal pain, swelling of the hands, fatigue, headache, palpitations, dizziness	Yes	Yes	Yes	-	-	-	Antibody
[4]	28	Male	Lethargy, weakness, shivering, muscular pain, headache, palpitation, dizziness	Yes	-	Yes	-	-	-	Antibody
[5]	27	Male	Fever, night sweat, shivers, stiffness, headache, dry cough, dizziness	Yes	Yes	Yes	-	-	-	Antibody
[6]	27	Male	Fever, headache, pain, sweating, cough	Yes	Yes	Yes	-	-	-	Antibody
[6]	37	Female	Fever, headache, sore throat, pains, cough	-	Yes	Yes	-	-	-	Antibody
[7]	30	Female	-	-	-	-	-	-	-	Antibody
[8]	43	Female	Fever, headache, nausea, diarrhea	Yes	Yes	-	-	-	-	Antibody
[9]	34	Female	Fever, malaise, fatigue, palpitation, arthralgia, headache, dizziness	Yes	Yes	Yes	Yes	Yes	-	Antibody
[10]	34	Female	Fever, jaundice, anemia	Yes	Yes	Yes	-	-	-	Immunoelectrophoresis
[11]	18	Male	Vomiting, fever, lethargy	Yes	Yes	-	-	-	-	Antibody in situ hybridization
[12]	23	Female	Low back pain, arthralgia, fever, nausea, vomiting, diffuse abdominal pain	Yes	Yes	Yes	-	Yes	Yes	Antibody
[13]	36	Female	Fever, myalgia, malaise	-	Yes	Yes	-	-	-	Antibody, PCR
[14]	19	Male	Malaise, anorexia, night sweats	-	Yes	Yes	-	-	-	Antibody, PCR
[15]	27	Female	Arthralgia, pharyngitis, cough, nausea, vomiting, diarrhea	Yes	-	Yes	-	-	-	PCR
[16]	22	Female	Anemia, jaundice	-	-	Yes	-	-	-	Antibody
[17]	28	Male	Leg pain, fatigue	-	Yes	-	-	-	Yes	Antibody
[18]	19	Female	Fever, malaise, urinary frequency	Yes	Yes	Yes	-	-	Yes	Antibody, PCR
[18]	27	Female	Fever, malaise, splenomegaly	Yes	Yes	Yes	-	-	-	Antibody, PCR
[19]	19	Female	Nausea, vomiting, dyspnea, sever fatigue, anemia	Yes	Yes	-	Yes	-	Yes	Antibody, PCR
[20]	34	Female	Presyncope, fever, myalgia	-	Yes	Yes	-	-	-	Antibody, PCR
[21]	34	Female	Anemia, fever	-	Yes	Yes	Yes	-	Yes	Antibody
Present case	33	Female	Fever, fatigue, nausea, anemia	-	Yes	Yes	Yes	-	Yes	Antibody, PCR

A hyphen shows that there is no evidence or no description of each characteristic on the article.
HS, hereditary spherocytosis; HPV, human parvovirus; PCR, polymerase chain reaction.

report, the median patient age was 38 years, with 86.7% aged 26–45 years [22], while in another report [23], the median age was 32–43 years (average, 38.0 years) for males and 15–43 years (average, 34.2 years) for females. Most individuals are infected with HPV-B19 during their school years, and the percentage of those with measurable levels of B19-specific IgG increases with age. More than 70% adults have measurable levels of B19-specific IgG antibodies [24,25]. Permanent immunity from HPV may decrease the incidence of viral infection in older patients with HS.

These cases were more frequently reported in females than in males. In the epidemiologic study of HPV-B19 infection-induced aplastic crisis in 308 children with homozygous sickle cell disease, the number of infected patients did not differ between genders [26]. The analysis of HPV-B19-induced epidemic acute red cell aplasia in 26 patients, primarily in children with hereditary hemolytic anemia (including only 1 patient with HS), included 14 males and 12 females [27]. In contrast, in a retrospective study of 30 immunocompetent patients infected with parvovirus B19 in Kyoto, the male:female ratio was 4:26 (86.7% were female) [22]. Another retrospective study of 21 healthy, adult patients with HPV-B19 infection included 4 males and 17 females [23]. In humans, the genetic background probably accounts for the different patterns of HPV-induced anemia, and host genes may regulate the outcome of HPV-B19-induced aplastic crisis [28]. One may speculate that a correlation exists between genetic differences and gender gap in association with susceptibility to HPV infection, although very little is known with regard to this field.

Fever, nonspecific flu-like symptoms [1], and abdominal symptoms such as nausea or vomiting, abdominal pain, and diarrhea may occur in patients with HPV-B19-induced aplastic crisis [27]. Abdominal symptoms were also commonly observed in our review. In contrast, abnormal liver function test results during HPV-B19 infection was documented in limited cases. In pediatric patients, elevated levels of hepatic aminotransferases may accompany the fifth disease, and parvovirus infection has been associated with severe but self-limited hepatitis [29]. However, parvovirus B19 could not be implicated in a large number of adult patients with acute or chronic hepatitis [1]. The precise incidence of liver enzyme dysfunction that occurs during HPV-B19 infection in adult patients with HS is uncertain; therefore, further investigation is required. In a clinical scenario, because the development of bilirubin gallstones is a common complication of HS with chronic hemolysis, HPV infection should be considered as a part of the differential diagnosis of hepatobiliary tract infection in patients with HS since fever, abdominal pain, and liver enzyme dysfunction will also occur with such infection.

Documentation of skin manifestation was less frequent and may be considered to have less diagnostic value for HPV infection in adults. Similar to the fifth disease [1], although the skin rash is a well-known symptom, it is less characteristic in adults. In the report including 22 children with sickle cell disease or HS, no skin rash was observed during parvovirus B19-induced aplastic crisis [30]. The pathogenesis of the HPV-B19 infection-induced rash remains unclear. Because it usually coincides with the production of measurable serum antibody, it is presumed to be at least partially immune mediated [31-33]. Different immune reactions according to age may be associated with the varying incidences of skin reaction; however, the precise reason remains unclear.

HPV-B19 infects erythroid progenitor cells and inhibits erythropoiesis, leading to acute erythroblastopenia and reticulocytopenia [34]. The bone marrow in patients with transient aplastic crisis is characterized by an absence of maturing erythroid precursors and presence of giant pronormoblasts [1]. Although giant pronormoblasts are suggestive of parvovirus B19 infection, they are not diagnostic of the disease [21,24]. Because of pancytopenia accompanied with a marked decrease in reticulocytes as well as a history of HS, it was natural to believe that the patient in the present case was suffering from aplastic crisis due to viral infection; therefore, we did not perform bone marrow aspiration. Bone marrow aspiration may not be routinely required when viral infection-induced aplastic crisis is highly suspected.

Conclusion

We report a case of aplastic crisis caused by HPV-B19 in an adult patient with HS. To the best of our knowledge, the current study is the first report that reviewed HPV-B19-induced aplastic crisis in several adult patients with HS. HPV-B19 infection-induced aplastic crisis is more common in young female patients with HS. Although fever or abdominal symptoms generally occur during HPV-B19 infection, skin manifestation may appear less commonly. It may be helpful to detect HPV-B19 infection by antibody or PCR methods to distinguish it from other infections, such as hepatobiliary infection due to gallstones, if suspected.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YK was responsible for the clinical management of our patient and preparation or writing of the first draft of the manuscript. YH and HK reviewed the manuscript and prepared the final draft. YI, HK and MT made substantial contributions to the acquisition and interpretation of clinical data. All authors read and approved the final manuscript.

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—【原　著】— Original —

ABO 血液型不適合腎移植におけるアルブミン製剤の必要性

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千野　峰子　岡田　真一　高源　ゆみ　青木　正弘　中林　恭子
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当院では輸血療法委員会や医師・看護師教育活動を通してアルブミン製剤適正使用を推進しているが，適正使用基準に到達しない状況が続いている．今回，アルブミン製剤の使用実態を使用場所別，使用目的別に検討した結果，年間使用量の約 12% は腎移植症例における血漿交換目的の使用であった．ABO 不適合移植では術前に 2 から 4 回程度の血漿交換により抗 A，抗 B 抗体価を低下させることが必要であり，また ABO 適合・不適合に拘わらず術後抗体関連拒絶反応を来たした場合には抗ドナー抗体の除去目的でアルブミンを用いた血漿交換は必須である．今回の検討でアルブミン製剤の平均使用量は ABO 血液型不適合腎移植で有意に多いことが明らかとなった．慢性腎不全患者の根治療法となりうる腎移植におけるドナー不足は深刻であり，ABO 血液型不適合腎移植の長期生着率は適合腎移植とほぼ同等の成績を得ていることから，今後も症例数の増加が見込まれる．この状況下で腎移植実施施設での輸血医療を適正に評価するために腎移植前後の血漿交換時におけるアルブミン製剤の使用は輸血管理料の算定基準の中で配慮することが望まれる．今後多施設共同で腎移植におけるアルブミン使用の実態調査を実施し，適正使用基準を新たに設定すべきと考えられた．

キーワード：血漿分画製剤，適正使用，血漿交換，慢性腎不全，臓器移植

はじめに

我が国のアルブミン製剤供給量においては適正使用の推進などにより 2008 年度まで減少を続けていたが，2009, 2010 年度は増加している．自給率は 2008 年度より低下し，2011 年度は 60% 未満に低迷している[1)2)]．アルブミン製剤の 40% 以上を輸入製剤に頼ることは，感染症のリスクや製造技術力の低下などの面から，日本の国民及び産業を守るためにも改善していかなければならない課題と思われる．また，少子高齢化に伴う献血者数が減少する一方で輸血を必要とする患者は増加し，輸血用血液製剤・血漿分画製剤の不足はより深刻な問題となる可能性がある．

輸血管理料は輸血管理体制を整備し適正使用の推進や安全な輸血の実施を目的とし，さらには輸血用血液製剤削減へとつながり輸血医療を維持していくために重要である[3)]．平成 24 年度診療報酬改定において，輸血管理料は輸血管理体制の整備に対する施設基準と適正使用加算となり，適正使用基準の FFP/RBC 比は 0.5 から 0.54，ALB/RBC 比は 2 未満となった．

当院は心臓血管外科手術や ABO 血液型不適合腎移植などの症例数が多いことを反映してアルブミン製剤の使用量が多く，2011 年での総使用量が 181kg に達している．同年の ALB/RBC 比は 2.53 であり，適正使用基準に至らない状況が続いていることから，今回当院におけるアルブミン製剤使用量が多くなっている要因を高張・等張製剤別，診療科別に分析し，更なる適正使用を図ることを目的として使用実態について調査検討したので報告する．

対象と方法

2007 年から 2011 年の赤血球製剤，新鮮凍結血漿，血小板製剤，アルブミン製剤の年間使用量を集計し，FFP/RBC 比，ALB/RBC 比の推移を検討した．2011 年に関しては使用されたアルブミン製剤を使用場所別に集計し，使用量の多い診療科については病棟・ICU 使用を等張・高張製剤別に比較した．高張製剤使用症例については使用前アルブミン値 3.0g/dl 以上で使用した症例，使用前アルブミン値 2.5g/dl 以上 3.0g/dl 未満で使用した症例から慢性低アルブミン血症における使用数を算出し，さらに詳しく適正使用状況を検討した．血液浄

東京女子医科大学輸血・細胞プロセシング部
〔受付日：2013 年 10 月 3 日，受理日：2014 年 4 月 4 日〕

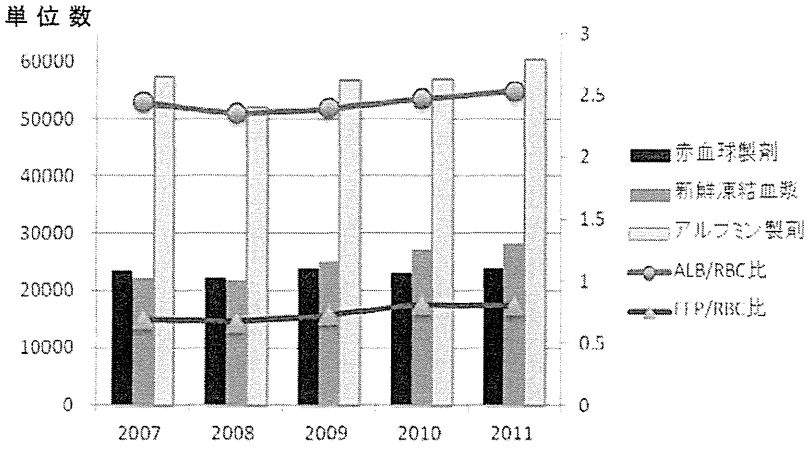

図1 2007年から2011年までのFFP/RBC比，ALB/RBC比の推移
過去5年間の赤血球製剤，新鮮凍結血漿，アルブミン製剤使用量，FFP/RBC比，ALB/RBC比を示す．棒グラフは赤血球製剤，新鮮凍結血漿，アルブミン製剤使用単位数，折れ線グラフはFFP/RBC比，ALB/RBC比を示している．血漿交換に用いたFFPが5,074単位であり，結果としてFFP/RBC比は0.80となった．一方，ALB/RBC比は2.53となり，FFP/RBC比，ALB/RBC比共に，輸血管理料Iの適正輸血基準を満たさなかった．

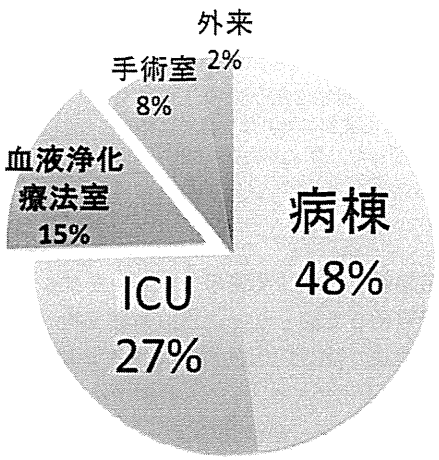

図2 2011年使用場所別アルブミン製剤年間使用量比率
2011年のアルブミン製剤使用量を使用場所別に分類した．全体の半数近くを病室にて使用し，次いでICU，透析室，手術室，外来となった．

化療法（透析）室にて使用されているアルブミン製剤についてはその使用目的と使用量を検討した．腎移植症例については2007年から2011年のABO血液型適合・不適合腎移植症例数および2011年のABO血液型適合・不適合腎移植の腎移植前後におけるアルブミン製剤平均使用量を算出し比較した．統計はStudent t-testを使用した．

結　果

当院における2007年から2011年の5年間の赤血球製剤，新鮮凍結血漿，血小板製剤，アルブミン製剤使用量（g数を単位数に換算）およびFFP/RBC比，ALB/RBC比の推移を比較した結果を図1に示す．赤血球製剤の使用量は大きな変化はなく，新鮮凍結血漿及びアルブミン製剤は増加傾向である．ALB/RBC比率は2009年より増加に転じており，現状では輸血管理料Iの適正輸血基準のALB/RBC比2未満には達していない．

2011年のアルブミン製剤使用量を使用場所別に比較した結果を図2に示す．総使用量の50%近くが病室にて使用されており，次いでICU，血液浄化療法室，手術室，外来の順であり，病棟およびICUでの使用が全体の75%ほどを占めていた．使用量の多い診療科4科の病棟・ICU使用量（g）を等張・高張製剤別に比較すると，消化器科と外科は病棟・ICUともに高張製剤の使用が多く，心臓血管外科は病棟では等張・高張製剤に大きな差はなかったが，ICUでは等張製剤が多かった．腎・泌尿器科は病棟では高張製剤が多く，ICUでは大きな差はなかった（図3）．

病棟・ICU使用総件数7,480件中84.6%が膠質浸透圧是正目的の使用であり，使用前アルブミン値3.0g/dl以上での使用は24.7%に達していた．診療科別では，消化器科311例（38.8%），心臓血管外科120例（15%），外科115例（14.3%），腎・泌尿器科99例（12.3%）となり，消化器科では慢性肝障害を基礎疾患とした難治性腹水，浮腫の改善を目的とした高張アルブミン製剤が特に多かった．アルブミン値3.0g/dl以下の低アルブミン血症に対する使用は75.3%であり，アルブミン値2.5以上3.0未満で複数回の使用があった症例465例中，

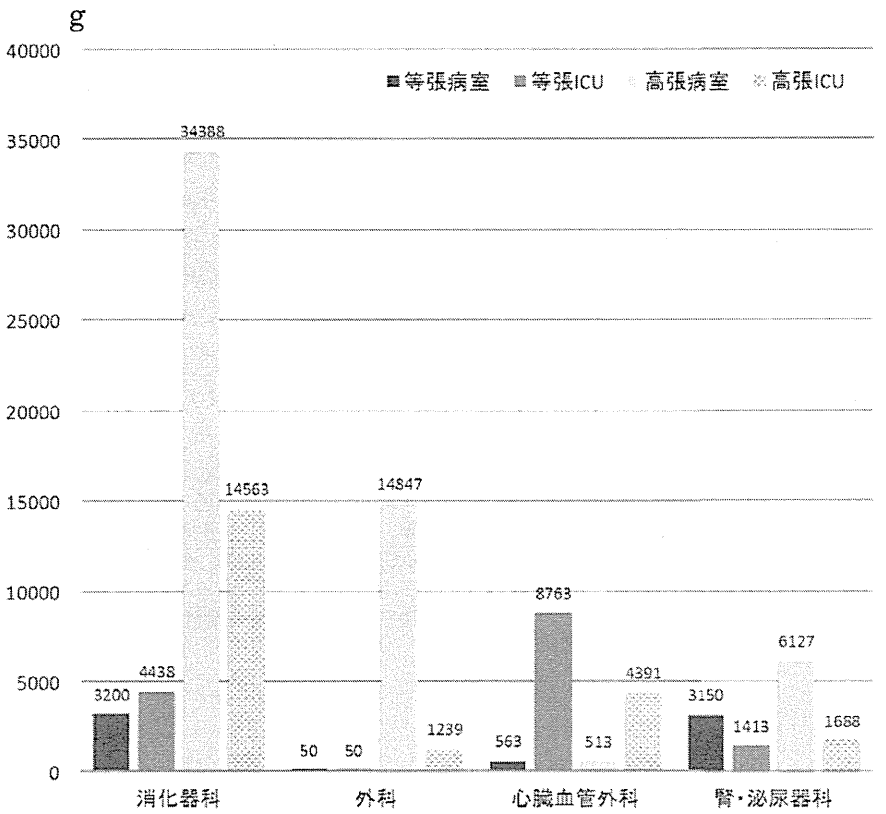

図3　アルブミン使用量の多い診療科の等張・高張製剤別使用量
消化器科，外科は病棟・ICUともに高張製剤の使用が多かった．心臓血管外科は病棟では等張・高張製剤に大きな差はなかったが，ICUでは等張製剤が多かった．腎・泌尿器科は病棟では高張製剤が多く，ICUでは大きな差はなかった．

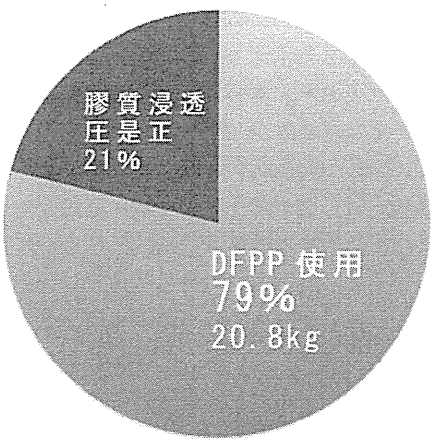

図4　血液浄化療法室におけるアルブミン製剤の使用目的別割合
血液浄化療法室にて使用されているアルブミン製剤の使用目的別割合を示す．二重濾過血漿交換療法目的のアルブミン製剤使用量は全体の79%を占めていた．

アルブミン値の追跡から急性低アルブミン血症とは認められない症例が154例（33.1%）存在し，これらの症例を不適正とすると，適正使用率は72.6%になった．

血液浄化療法室にて使用されているアルブミン製剤の使用目的を分類したところ，血漿交換（二重濾過血漿交換療法；DFPP）目的のアルブミン製剤使用量が全体の79%を占めており，この目的でのアルブミンの使用総量は20.8kg（全使用量の11.5%）となっていた（図4）．

ABO血液型不適合腎移植症例に関しては手術当日までに抗A，抗B抗体価16倍以下を目標として2から4回の血漿交換を実施していた．一方，ABO血液型適合・不適合に拘わらず腎移植前には抗ドナーHLA型抗体価の低下を目的とした血漿交換が必要となるケースがあり，適合腎移植例の約15%に血漿交換を必要とした．

2011年のDFPPにおけるアルブミン使用量が適正か否かを判断するために67例を対象にして，患者体重およびDFPP前のアルブミン値から算出されるIgG除去率70%を達成するのに必要な補充液量と補充液中アルブミン濃度を算出し，必要アルブミン量を求めた[4]．実際に使用されたアルブミン量（U）と必要アルブミン量（R）との比較では，67例中21例（31.3%）がU：Rが120%を超えていた．

2011年の腎移植症例における移植前後を含めたアル

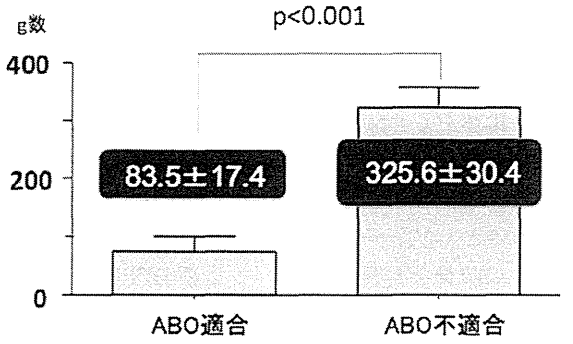

図5 腎移植症例のアルブミン平均使用量
2011年の腎移植症例における移植前後を含めたアルブミン製剤の平均使用量を示す．ABO血液型適合腎移植では83.5±17.4g，不適合腎移植では325.6±30.4gと不適合移植術で有意に多く使用していた．

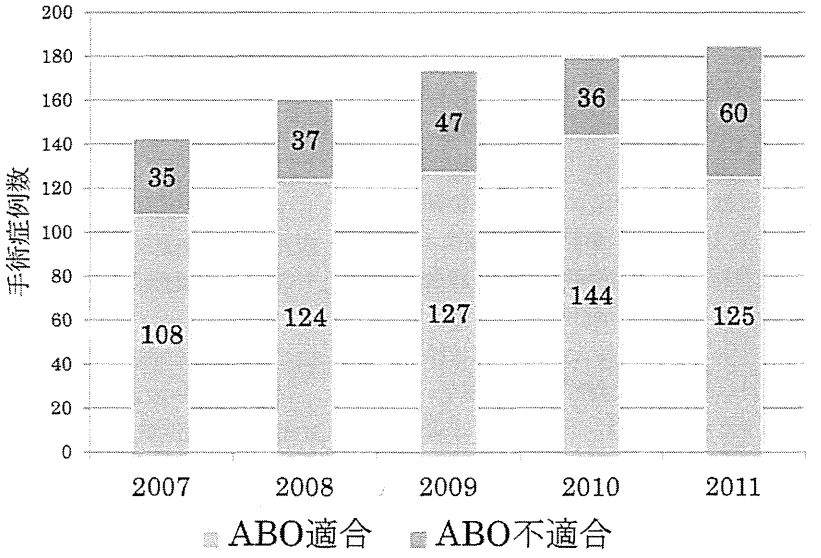

図6 東京女子医大病院における腎移植症例数
当院の過去5年間の腎移植症例数をABO血液型適合腎移植術，ABO血液型不適合腎移植術別に示す．腎移植症例数は143件から185件と増加傾向にあり，2011年では約1/3がABO血液型不適合腎移植であった．

ブミン製剤の平均使用量は，ABO血液型適合腎移植では83.5±17.4g，不適合腎移植では325.6±30.4gと不適合移植術で有意に多く使用していた（図5）．当院における過去5年間の腎移植症例数は143件から185件と増加傾向にあり，ABO血液型不適合腎移植術の全体数に対する割合も増加し，2011年では約1/3が不適合腎移植であった（図6）．

考　察

腎移植は慢性腎不全患者にとって腎機能の回復を目指すための安全で確実な根治的治療法であるが，登録日から移植日までの平均待機期間は約14年であり，ドナーの確保が我が国の腎移植にとって最大の問題点となっている[5]．ABO血液型不適合腎移植は，ドナー腎血管内皮細胞に発現されているABO血液型抗原に対してレシピエント血液内に存在する抗A，抗B抗体が反応することで惹起される拒絶反応を血漿交換によって克服することで可能になった[6]．その後，免疫抑制剤，摘脾術および移植前の血漿交換の併用によりAlexandreらは26例のABO血液型不適合生体腎移植で1年間の生着率88%という好成績を発表した[7]．東京女子医科大学の東間らはDFPPを利用することで8%アルブミンを含む置換液量を減少することに成功し，さらに抗A，抗B抗体価を16倍以下に低減することにより，長期の移植腎生着が達成できることを示した[8][9]．一方で近年の研究では移植前抗A，抗B抗体価は移植腎の拒