

Acute Pure Red Cell Aplasia Associated with Allopurinol Therapy

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Several investigators have reported patients with acute pure red cell aplasia (PRCA) caused by anticonvulsants, antibiotics, or antithyroid agents. Allopurinol is known to be a causative agent of aplastic anemia, but there have been few reports of acute PRCA induced by allopurinol. We describe here a 15-year-old boy who suffered from anemia 6 weeks after initiation of allopurinol therapy; his anemia immediately improved after cessation of the drug. His bone marrow showed severe erythroid hypoplasia with a myeloid/erythroid ratio of 18.6 and low expression of glycophorin A detected on cell-surface antigen analysis. No morphological abnormalities were observed in myeloid series and megakaryocytes. The prolonged plasma iron disappearance rate and the decreased plasma iron turnover rate also indicated erythroid hypoplasia. He had been free from any infections, including parvovirus B19, before manifestation of PRCA. Taken together, these results suggest a diagnosis of acute PRCA. This side effect of allopurinol should be taken into consideration. *Am. J. Hematol.* 61:209–211, 1999. © 1999 Wiley-Liss, Inc.

Key words: allopurinol; pure red cell aplasia; William's syndrome

INTRODUCTION

Pure red cell aplasia (PRCA) is a rare hematologic disorder characterized by the absence of erythroblasts in otherwise normal bone marrow [1]. PRCA can be classified into three types: an acute type and chronic type, either constitutional or acquired. Acute PRCA associated with infections is relatively common, because PRCA is often preceded by a febrile illness with either upper respiratory complaints or gastroenteritis. Acute PRCA has also been considered to be related to the toxicity of drugs. However, the exact method for making the diagnosis of drug-induced PRCA is not well established; therefore, the diagnosis has often been based on clinical course. The common causative drugs of acute PRCA described in the literature were anticonvulsants, antibiotics, and antithyroid agents [1–4]. As far as we know, there have been few reports of acute PRCA induced by allopurinol, an inhibitor of uric acid biosynthesis [5,6]. We report here the case of acute PRCA, presumably caused by allopurinol, in a child with William's syndrome.

CASE REPORT

The patient was a 15-years-old boy and diagnosed with Williams syndrome at an infant. He had total anomalous pulmonary venous return (TAPVR) and chronic congestive heart failure. Surgical correction of TAPVR was performed at the age of 13. Because of the congestive heart failure, he started to receive furosemide, spironolactone, and digoxin 2 years ago. He was found to have hyperuric acidemia (6.9 mg/dl) of unknown origin 2.5 years ago. Allopurinol was started at a dose of 200 mg per day, because his uric acid level was elevated to 9.5 mg/dl. Six weeks after initiation of allopurinol therapy, he developed anemia and was admitted to our hospital. During allopurinol therapy, his renal function

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TABLE I. Laboratory Findings*

WBC	6.1×10^9	/l	GOT	67	IU/l	HbF	1.9	%
seg.	66	%	GPT	144	IU/l	EPO	157	mU/ml
lym.	15	%	LDH	300	IU/l	NAP (%)	77	%
mono.	14	%	T-Bil	1.4	mg/dl	NAP score	242	
eosi.	3	%	Fe	269	μ g/dl	ANAb	(-)	
baso.	2	%	UIBC	25	μ g/dl	PIDR-t1/2	45	min
RBC	202×10^{12}	/l	Ferritin	680	ng/ml	PIT	0.5	mg/kg/day
Hb.	6.5	g/dl	Haptoglobin	57.7	mg/dl	% ⁵⁹ Fe-utilization	98	%
Ht.	21.9	%	D-coombs	(-)		RCIT	0.5	mg/kg/day
MCV	90.6	fl	HAM test	(-)		DLST		
MCH	32.2	pg	Sugar water	(-)		allopurinol	717	cpm
MCHC	35.5	%				control	449	cpm
Plt.	214×10^9	/l				SI	1.60	
Reti.	1.6	%						
BM-aspiration						HBs Ag	(-)	
NCC		55.0×10^9	/l			HBs Ab	(-)	
Erythroid series		3.8	%			HAV-Ab	(-)	
Myeroid series		67.2	%			HCV-Ab	(-)	
Eosin. series		3.2	%			Parvo B19 IgG	6.28 (day 2) 5.58 (day 7)	
Mono. series.		0.2	%			Parvo B19 IgM	0.14 (day 2) 0.27 (day 7)	
Lym. series		20.2	%			Parvo B19 PCR	(-)	
Plasma cell		0.2	%			25-AS	22	pm/dl
morphological abnormality		(-)						
Chromosomal analysis		46, XY						

*EPO, erythropoietin; NAP, neutrophil alkaline phosphatase; ANAb, antinuclear antibody; PIDR, plasma iron disappearance rate; PIT, plasma iron turnover rate; RCIT, red cell turnover rate; 25-AS, 2',5'-oligoadenylate synthetase (normal range, <130); DLST, drug-lymphocyte stimulating test; SI, stimulating index; NCC, nuclear cell count.

was normal (serum creatinine: 0.4–0.6 mg/dl, serum BUN: 11–17 mg/dl, serum Ca: 8.8–9.4 mg/dl, and the clearance of creatinine: 86–90 ml/min). On admission, hepatomegaly, edema on lower extremities, puffy eyelids, labored respiration, midsystolic heart murmur, pale lips, and anemic palpebral conjunctiva were observed. Bone marrow (BM) aspiration and BM biopsy revealed mild hypoplasia, and almost absent erythroid precursors (myeloid series/erythroid series ratio was 18.6). Cell-surface antigen analysis of the BM cells showed 8.7% positivity for glycophorin A. Decreased incorporation of ¹¹¹In to BM also suggested hypoplasia of BM. The plasma iron disappearance rate (PIDR-t1/2) was prolonged to 45 min. Plasma iron turnover rate (PIT) and red cell iron turnover rate (RCIT) were decreased and showed incorporation of radioisotope to the spleen, indicating selective erythrocyte aplasia (Table 1). We diagnosed him as having PRCA. None of the antibody titers against hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), or parvovirus B19 were elevated. Neither polymerase chain reaction analysis of parvovirus B19 nor 2',5'-oligoadenylate synthetase (2'5'-AS) level was positive. Because we thought that allopurinol was a causative agent of PRCA, we stopped allopurinol therapy. Reticulocyte counts immediately increased and anemia improved thereafter (Fig. 1). There has been no recurrence of anemia.

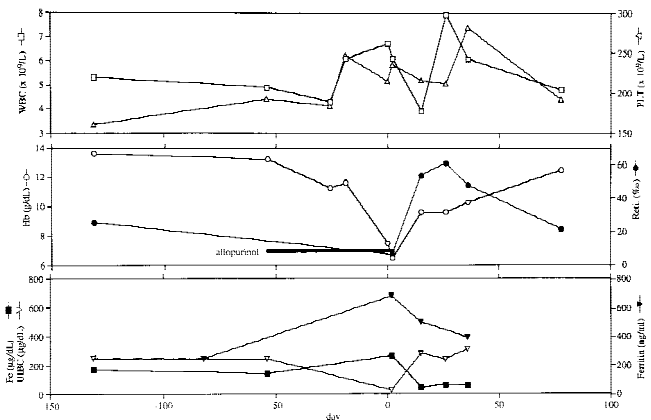


Fig. 1. Clinical course of the patient. Day 0 indicates the date of admission to our hospital. WBC, white blood cell count; PLT, platelet count; Hb, hemoglobin; Reti, reticulocyte; UIBC, unbound iron binding capacity.

DISCUSSION

Eighty percent of acute PRCA is considered to be associated with infection, and the remaining 20% is drug induced. In addition, 60% of infection-associated acute PRCA is caused by parvovirus B19 [1]. Other causative viruses are HAV, HBV, HCV, herpes simplex virus, herpes zoster virus, Epstein-Barr virus, and cytomegalovirus [1–3]. Our present case had not had previous infectious episodes due to these viruses, as judged by both deter-

mination of antibody titers and polymerase chain reaction analysis of parvovirus B19. Drug-induced acute PRCA has been reported to be caused by anticonvulsants, antibiotics, and antithyroid agents [1–4]. A review article by Dessypris [5] has listed allopurinol as a causative drug of PRCA, but the precise information has not been described. The only case report of PRCA induced by allopurinol we have found in the literature was an adult patient described by Vohra *et al.* [6]. Our patient developed anemia 6 weeks after allopurinol therapy was initiated, and immediately improved after cessation of the drug. Therefore, it is quite possible that acute PRCA in this patient was caused by allopurinol.

Although previous investigators have postulated an important role of anti-erythroblast antibody, anti-erythropoietin antibody, or T-cell-mediated inhibition of erythropoiesis in acute PRCA, the exact mechanism of acute PRCA by drugs has not been clarified [7–10]. Watts *et al.* have reported that the *in vitro* colony formation of BM cells was inhibited by valproate without serum from patients with valproate-induced PRCA [11]. On the other hand, Fox *et al.* have reported that allopurinol decreased phosphoribosylpyrophosphate in erythrocytes and inhibited purine biosynthesis. Purine nucleotide biosynthesis is considered to play a role in cell viability of dividing erythroblasts [12]. It is worth noting that azathiopurine, another inhibitor of purine metabolism, has been well documented as a causative agent for PRCA [4]. Other investigators have suggested that aplastic anemia might be the allopurinol-induced hematologic toxicity [13–15], indicating that allopurinol affects the maturation of BM cells other than erythroid series. Finally, allergic reaction to allopurinol cannot be ruled out at present. But the lymphocyte stimulation test for allopurinol was negative.

In summary, we describe the case of a child with acute

PRCA, probably due to allopurinol therapy. This must be a rare event, but this side effect should be taken into consideration, especially in patients having impaired metabolism of the drug [14].

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