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Original Article

Long-term outcome of pregnancy complicating with severe aplastic anemia under supportive care

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ABSTRACT

Objectives: Pregnancy associated with aplastic anemia (AA) is a rare and heterogeneous disorder. We aimed to identify and evaluate the maternal and pregnant outcomes of pregnancy-associated severe AA treated with supportive care.

Materials and methods: A 25-year retrospective study was conducted at in a single center between 1990 and 2014 with pregnancy associated severe AA. In addition, relevant published cases of antenatally diagnosed pregnancy-associated severe AA after 1990 were identified by PubMed. The main goal was to determine the impact of various risk factors on maternal and fetal outcomes.

Results: 15 women with 18 pregnancies were enrolled. With addition of the published reports in literature, a total of 36 cases were included for reference review. Univariate analysis showed that low platelet counts (<2.0 × 10^9/L), bone marrow hypocellularity (<25%), and late diagnosis during pregnancy were predictors of poor maternal outcomes ($P < 0.05$). The complication rate of pregnancy outcomes was 53.3%, including preterm delivery, small gestational age (SGA), preterm premature ruptured of membranes (PPROM) and preeclampsia.

Conclusions: This study identified the risk factors of mortality and morbidity in pregnant women with severe AA, as well as the obstetrical complications associated with neonatal outcome.

Introduction

Aplastic anemia is a rare and potentially life-threatening disorder, especially for women during pregnancy [1,2]. Aplastic anemia can be either acquired or congenital. The inciting factors of acquired AA include radiation, drugs, infection and organic compounds. Some studies proposed the hypothesis indicating that pregnancy is a risk factor; however the exact pathophysiology between pregnancy and AA is still controversial [3–5]. The risk to pregnant women is focused on hemorrhage and uncontrolled sepsis due to pancytopenia. The true mechanism and pathophysiology of AA is still unclear [2], but it is generally considered as an autoimmune disorder [1]. Immunosuppressive agents or hematopoietic stem cell transplantation are contraindicated during pregnancy because the potential toxicity to fetus [3,5]. Supportive care is the mainstay of treatment in pregnancy, and the prognosis is better than it was several decades ago, largely because of better supply of blood products [5]. Meanwhile, the fetus would also suffer from high risk of preterm delivery, growth restriction or intrauterine fetal death as a consequences resulted from maternal morbidity [6]. Thus, a pregnancy complicated by severe AA is a great challenge for obstetricians.

The present study summarized the data on prenatal and postnatal conditions of 15 cases of pregnant women and 18 pregnancies which with the diagnosed of pregnancy-associated severe AA. By pooling our data with a review of published cases, we aimed to evaluate outcome of pregnancy-associated severe AA and investigated the factors that could be associated with poor maternal outcomes during and after pregnancy.

Materials and methods

A retrospective study was conducted by compiling all patients between 1990 and 2014. Fifteen cases were diagnosed and received treatment as pregnancy-associated aplastic anemia in the

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Department of Obstetrics and Gynecology, Chang Gung Memorial hospital. Cases that had ongoing disease during pregnancy and received abortions were excluded. There were no inciting factors such as infection, irradiation, leukemia and immunological disorders in these cases [7]. We reviewed the characteristics included age, parity, delivery (gestational age and mode), baseline hematocrit, complications of pregnancy. The diagnosis of pregnancy-associated severe AA was made according to the diagnostic criteria proposed by Brodsky et al. [1]. Severe aplastic anemia was diagnosed as bone marrow biopsy showing less than 25 percent of normal cellularity or less than 50 percent normal cellularity in which fewer than 30 percent of the cells are hematopoietic and at least two of the following are present: absolute reticulocyte count below 40,000/microliter; absolute neutrophil count (ANC) less than 500/microliter; or platelet count below 20,000/microliter [8]. Bone marrow aspiration was done in each woman in present study.

To make definite diagnosis of aplastic anemia, other etiologies of cytopenias, such as paroxysmal nocturnal hemoglobinuria (PNH), large granular lymphocyte leukemia, myelodysplastic syndromes (MDS), marrow replacement by fibrosis or tumor, severe megaloblastic anemia, acute leukemias, and overwhelming infection due to HIV or the viral hemophagocytic syndrome were excluded carefully by bone marrow biopsies and clinical manifestations.

Seven of the 15 cases had a known history of severe AA and 8 cases were diagnosed severe AA during prenatal clinic, underwent visits at every one to two-week interval based upon the severity of clinical manifestations. Steroids were used while blood transfusion with leukocyte-free PRBC and platelets were given during prenatal period to maintain the hemoglobulin level higher than 8 g/dL and platelet counts greater than 20×10^9/L. Clinical data and obstetric surveillance decided the timing and mode of delivery. After delivery, the patients underwent postpartum care at every 2 weeks in the first 2 months. Complete remission (CR) was defined as neutrophil counts greater than 2.0×10^9/L and platelet counts greater than 100×10^9/L. Partial remission (PR) was defined as neutrophil counts higher than 1.0×10^9/L and platelet count greater than 30×10^9/L. Non-responder (NR) was defined as patients who required blood transfusion to maintain the neutrophils and platelet counts [9].

Detailed follow-up information on each case was obtained in all instances through medical records and/or telephone interviews with the physicians.

Statistics

The results were shown as percentages for frequencies, and as means for variables. The data were analyzed using the SPSS 12.0 statistical package (Chicago, IL, USA). Fisher's exact test was used to evaluate the significance of differences between designated groups. $P < 0.05$ was considered statistically significant.

Results

The demographics of the 15 cases of pregnancy-associated aplastic anemia from our hospital were shown in Table 1. The maternal and neonatal outcomes were presented in Table 2. In the 18 pregnancies, one case suffered from preterm premature ruptured of membranes at 22nd weeks of gestational age and had to terminate the pregnancy due to severe oligohydramnios. To analyze the complications during the 17 survival pregnancy, preterm birth (<37 weeks) was 41.2% (7/17), small gestational age was 11.8% (2/17), preeclampsia was 5.9% (1/17) and PPROM was 17.6% (7/17). 17 deliveries had babies survived without major complications (Table 3).

Of the 15 pregnant women, 3 cases died within five years after delivery, with one at 2 weeks, one at a year and one after four years later due to disease progression to myelodysplastic syndrome and uncontrolled sepsis. 9 of 12 survival cases were under status of complete remission (CR) and the other 3 cases were in partial remission (PR). The mean maternal age was 31.7 years (range 22–38). The mean follow-up period was 48.9 months (range 12–184 months) (Table 3).

In the pooled analysis which included the data from literature reports, there were 31 cases with pregnancy-associated severe AA enrolled by review of literature [3–5]. Adding our 15 cases gave a total of 46 cases. Five patients were excluded from the analysis because the detail individual outcomes of interest were not specified. Five cases were excluded due to loss follow-up. The detailed study design was summarized in Fig. 1. Thus, 36 cases were included for analysis and we categorized into two groups. The group A included 27 patients with an uneventful maternal outcomes (complete remission or partial remission) and group B included 9 complicated pregnancies (3 cases of non-responder and 6 cases of maternal death). The two groups differed in prenatal clinical courses and pregnancy outcomes.

Table 1
Clinical and hematological profile of the 18 pregnancies at presentation.

Case no.	Age (years)	Parity	GA (weeks)	Hb (g/L)	WBC ($\times 10^9$/L)	Neutrophil ($\times 10^9$/L)	PLT ($\times 10^9$/L)	BM (%)
1	29	1	9	7	3.8	1.8	29	20
2	33	1	27	3.7	3.9	2.3	15	5
3	28	1	11	7.4	3.4	1.7	14	20
	35	2	7	9	4.5	2.4	49	
4	35	2	16	7.4	2.2	0.8	11	15–20
5	24	1	22	9.3	2.7	1.8	34	25
6	22	1	18	6.5	3.1	1.0	4	20
7	38	1	26	9.9	3.4	2.0	36	30
8	31	1	36	9.3	5.0	3.3	45	30
9	28	1	21	8.4	3.9	2.4	32	15–20
	31	2	10	7.3	3.8	1.3	22	
10	34	1	13	2.1	4.9	2.8	17	20
11	31	0	35	6.7	3.8	1.8	14	25
	34	1	11	6.4	3.4	1.6	18	
12	31	1	26	4.4	3.4	1.9	8	15
13	35	0	8	10.6	4.6	2.7	29	10
14	37	1	37	9.3	5.0	3.1	45	25
15	34	0	11	6.5	2.8	1.1	12	20

Abbreviations: BM, bone marrow; GA, gestational age of diagnosis; Hb, hemoglobin; WBC, white blood cell count; PLT, platelet count.

Table 2
Clinical course and final outcome of the 18 pregnancies.

Case no.	GA	Delivery	BBW	Association problems	Neonatal outcome	Follow up	Maternal outcome
1	38	CS	2880		Alive	84	PR
2	32	CS	1760	Preeclampsia	Alive	11	Expired
3	38	CS	2922		Alive	34	PR
	38	CS	2678		Alive	23	PR
4	38	CS	2980		Alive	168	CR
5	37	CS	2240		Alive	184	PR
6	36	SD	2720		Alive	48	Expired
7	36	CS	2980		Alive	36	PR
8	36	CS	2720	PROM	Alive	42	Expired
9	37	CS	3120		Alive	36	PR
	38	CS	3460		Alive	34	PR
10	37	CS	2680		Alive	24	PR
11	36	CS	2820		Alive	18	CR
	28	CS	920/1260	PROM	Alive	36	CR
12	34	CS	2380	PROM	Alive	38	PR
13	38	CS	3920		Alive	12	CR
14	39	CS	2820		Alive	13	PR
15	22	SD	240	PROM	Expired	48	PR

Abbreviation, GA, gestational age at delivery; BBW, birth body weight; PROM, preterm premature ruptured membranes; CS, Cesarean section; SD, Spontaneous delivery; PR, Partial Remission; CR, Complete Remission.