Aplastic anemia (AA) is a rare disease characterized by pancytopenia and hypocellular bone marrow. Three decades ago, the same topic of this editorial was discussed by Neal Young, National Institute of Health, in British Journal of Haematology [1]. He tried to address the following question: ‘Is aplastic anemia in Asia really the same diseases as aplastic anemia in the Western countries?’ He stated in the article that he was very impressed by the large number of new patients seen at tertiary hospitals in Thailand and China. AA in Asia was characterized by higher incidence and prevalence of moderate AA.

Recently, I visited the Institute of Hematology and Blood Diseases in Tianjin, China, and was surprised to know that more than 200 new patients with AA were admitted to the hospital every year. To achieve a consensus of diagnostic criteria, we conducted a joint review of bone marrow smears and trephine biopsies in 100 children with acquired bone marrow failure syndrome according to the World Health Organization (WHO) classification between Tianjin and Nagoya [2,3]. No significant differences between Japanese and Chinese patients were found with regard to clinical and laboratory findings or the distribution of diagnosis. The incidence of AA appears to be two to three times higher in Asia than Europe and North America, where yearly incidence rates are approximately 2.0/million/year [4]. While the incidence of AA was investigated in several countries, most of these studies were conducted more than 20 years ago and both adult and pediatric cases were mixed. Jeong et al. reported the registry data of AA patients younger than 15 years old in Korea [5]. Between 1991 and 2005, a total of 828 patients were registered. The incidence of childhood AA was 5.16/million/year. The degree of disease severity was specified in 780 patients; 456 (58%) and 328 (42%) patients suffered from severe and non-severe AA, respectively. Forty-four patients were diagnosed with constitutional anemia including 40 patients with Fanconi anemia. Jeong et al. reported that the proportion of patients attributable to exposure to drugs was only 5%, which resulted in the conclusion that use of drugs did not explain the relatively high incidence of AA in Japan [6].

The incidence was 4.79/million/year. The severe/non-severe ratio was 56% versus 44%. A total of 178 (10.8%) patients had hepatitis-associated AA and most of other patients were diagnosed as idiopathic AA. During the same period, 111 patients with Fanconi anemia were registered. Even now, Dr Young’s description is true that incidence of AA, especially, non-severe type is higher in Asia than in the West.

Why is the incidence of AA higher in Asia than in other areas? Several investigators tried to address this question. Drugs and toxin exposure and indigenous viruses were discussed as the possible explanations. However, medical drugs are uncommon causes of AA in Japan and Korea. A population-based, case-control study in Thailand also revealed that the proportion of patients attributable to exposure to drugs was only 5%, which resulted in the conclusion that use of drugs did not explain the relatively high incidence of AA in Thailand [7]. Also, although East Asia is a hepatitis prevalent area, incidence of hepatitis-associated AA in Asia is not so high compared to in Europe [8,9]. One possibility is high incidence of cryptic type of inherited bone marrow failure syndromes including Fanconi anemia and dyskeratosis congenita (DC) in Asian population. In Japan, all AA children were screened by chromosome breakage assay and test for telomere length for these 10 years. Also, only 2% of patients with idiopathic AA were diagnosed as cryptic DC by sequencing of telomere complex genes [10]. Our data does not support this possibility.

MaCahon et al. investigated the incidence of acquired AA in British Columbia, Canada, and found the higher incidence of AA in East and South-East Asia descent (6.9/million/year) than those of white/mixed ethnic descent(1.7/million/year), which suggested a genetic disposition rather than environmental factors [11]. AA is considered as an immune-mediated disease. The risk of development has been linked to host genetics such as human leukocyte antigen (HLA) types and nucleotide polymorphisms in some cytokine genes. It has been found that there is a significant increase in the frequency of several HLA types in the Asian AA patients which were not observed in the white/mixed AA patients. A study from Tianjin showed that certain types of HLA loci contributed to the susceptibility and severity of AA in China [12]. Also, some AA patients have polymorphisms which are linked to high production of tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma [13]. Homozygosity for [12] CA repeats in the first intron of the IFN-
gamma gene is strongly associated with the risk of AA in Caucasian subjects [14]. It should be done to study the frequency of this genotype in Asian population. Patients with reduced ability to metabolize environmental toxins may be at risk of developing AA. Genetic polymorphisms of detoxing enzymes such as glutathione S-transferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1) were studied in AA patients by several groups. The incidence of GSTM1 and GSTT1 gene deletions was significantly higher in healthy Korean population compared to those of white Americans and African-Americans. Moreover, incidence of these deletions was significantly higher in AA patients than healthy controls in Korean populations, but no differences were seen between AA patients and healthy controls in Caucasian population [15,16]. These findings may explain the higher incidence of AA in East Asia. It is interesting to elucidate the difference in the genetic background between Asian population and other populations using the latest technology such as next-generation sequencing.

The last possibility is the variation of diagnostic criteria between Asia and Western countries. Hypoplastic myelodysplastic syndrome (MDS) is sometimes very difficult to separate from moderate AA utilizing standard morphological criteria. As I mentioned, moderate AA is more common in Asia. Refractory cytopenia of childhood (RCC), one of childhood MDS, was proposed from the European Working Group of MDS (EWOG-MDS) in Childhood and accepted in WHO classification. According to this classification, diagnosis of AA is applied to the patients with complete aplasia or severe hypoplasia of hematopoiesis with scarcely distributed bone marrow cells without patchy areas. Presence of dysplasia on morphology and chromosome abnormalities was also taken into account. Because most of the patients with moderate AA have residual hematopoiesis in the bone marrow, diagnosis of moderate AA before the introduction of WHO classification may change to RCC. Before the proposal of RCC by WHO classification, we conducted a prospective study with antithymocyte globulin and cyclosporine for children with both moderate and severe AA, which provides a unique opportunity to compare the clinical outcome between RCC and AA. We retrospectively classified the 190 patients having reserved bone marrow smears and trephine biopsies according to WHO MDS classification [17]. Only 62 (33%) patients were classified as AA and the remainder was classified as RCC. The diagnosis was changed to RCC in considerable percentage of patients with AA since the introduction of WHO classification 2008 in Japan. So, the difference of diagnostic criteria may affect the frequency of AA to compare the incidence between Asia and Europe. Chinese investigators also retrospectively classified 130 children with acquired bone marrow failure according to WHO classification [18]. The final diagnoses were RCC in 78 patients (60%) and AA in 52 patients (40%). The incidence of AA is no longer different if we use diagnostic criteria proposed by WHO. AA is considered as an immune-mediated process and RCC as clonal stem cell defect. Surprisingly, our study did not show any difference of response rates to immunosuppressive therapy (IST) and cumulative incidence of clonal evolution between AA and RCC. In a Chinese study [18], the response rate to IST in RCC patients (75%) was higher than that of AA patients (38%).

Since 2009, we have prospectively reviewed bone marrow morphology of children with idiopathic bone marrow failure and inquired the outcome of the patients. Among 451 patients, 98 (22%) were classified as AA and 353 (78%) as RCC. Also, the response rate to IST was not different between both groups. Yoshimi et al. in EWOG reported the response rates to IST in patients with both RCC and AA [19,20]. The response rates at 6 months were somewhat higher in patients with RCC than AA. Moreover, our recent study using next-generation sequencing indicated that incidence of somatic mutations was not different between AA and RCC. The proposal of a new clinical entity should be based on the pathobiology and prediction of clinical outcome. In this sense, RCC classification warrants further studies to be used widely in the world, which is critical to estimate the incidence of AA.

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