

## EDUCATION SESSION 3: APLASTIC ANEMIA



### Aplastic Anemia: Epidemiology

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Aplastic anemia is a bone marrow failure syndrome characterized by peripheral blood pancytopenia and marrow hypocellularity. It has been believed that aplastic anemia is rare in the West and is more common in Asia. This belief is based on the number of patients seen at a single large referral hospital. However, only few reliable incidence studies have been reported.

Aplastic anemia was first reported to be associated with chloramphenicol. Later on, several case-reports described its associations with drugs, chemicals and viral infections. Prevention of the disease is of importance because it is a serious disorder and treatment with stem cell transplantation or immunosuppressive agents is expensive. Possible risk factors have been identified in population-based case-control studies. However, there is heterogeneity in the etiology and the pathogenesis of aplastic anemia among cases.

#### **Incidence**

Aplastic anemia is more common in the Orient; the number of patients seen at a large referral hospital in Asia exceeds the number in the West<sup>[1]</sup>. In Thailand, at Siriraj Hospital in Bangkok 60–70 new cases are seen annually and more than 1,500 cases have been documented in our hematological clinic. There were 40 patients per annum at the Chinese Academy of Medical Science, Tienjin, China and 18 annually at Kyungpook National University Hospital, Korea. In the USA, at the University of Virginia, the number was 2.3; at the University of Utah and Salt Lake City Veterans Administration Hospital it was 4.2. The number of patients seen at two large referral hospitals in Europe is higher; 20–30 per annum at St George's Hospital in London and 15–20 per annum at Hôpital St Louis in Paris. In Thailand, aplastic anemia appears to be as common as acute leukemia in the Orient, whereas acute leukemia is 5–10 times more common than aplastic anemia. The number of patients does not reflect the true incidence of the disease but rather reflects the referral pattern.

Accurate determination of the incidence of aplastic anemia requires active case ascertainment to identify all new cases over time and accurate diagnosis based on characteristic bone marrow pathology. Three major population-based

studies of aplastic anemia have been conducted recently; the International Agranulocytosis and Aplastic Anemia Study (IAAAS); the French Cooperative Group Study; and the Thai Aplastic Anemia Study Group.

The annual incidence in Bangkok was 3.9 cases per million<sup>[2]</sup>. It was higher in Khonkaen at 5.0 per million and lower in Songkla at 3.0 per million<sup>[3]</sup>. These incidence rates are higher than those reported by the IAAAS (2.0 per million in Europe and Israel)<sup>[4]</sup> and the French Cooperative Group Study (1.4 per million in France)<sup>[5]</sup>. The geographic differences among regions may be due to different distributions of risk factors.

The pattern of the age incidence is consistent in the West with an increase in incidence with increasing age. In Bangkok, there were two peak age incidences: 6.8 per million at the 15–24 year age group, almost four times higher than that observed in the IAAAS, and 7.7 per million at least 60 years old<sup>[3]</sup>. The high incidence among the younger age group in Bangkok suggests the possibility of unique environmental or occupational exposure. The age distribution in Khonkaen and Songkla was similar to those in the West.

#### **Etiologic Factors**

##### **1. Drugs**

Drugs are the most important cause of aplastic anemia<sup>[4]</sup>. Results obtained from a combined analysis of these three case-control studies indicate that there were 11 associated drugs; the most common drugs are penicillamine, gold, carbamazepine and non-steroidal anti-inflammatory drugs. The etiologic fraction due to drugs was 27% in the IAAAS.

Drugs are not common causes of aplastic anemia in Thailand<sup>[6]</sup>. The etiologic fraction for all associated drugs was low at 5%. The most common drugs include thiazide diuretics, sulfonamide, and mebendazole. There was no association with chloramphenicol. Other drugs that have been reported to be associated with aplastic anemia, including anti-inflammatory drugs and anticonvulsants, were not commonly used<sup>[6]</sup>.

## 2. Occupational factors

Agricultural pesticides have been reported to be associated with aplastic anemia in the IAAAS<sup>[4]</sup>. An increased risk was observed for exposure to agricultural pesticides in Khonkaen, involving and etiologic fraction of 10%<sup>[7]</sup>.

With regard to household pesticides, which are very commonly used in Thailand, there was no evidence that use of household pesticides increases the risk of aplastic anemia<sup>[8]</sup>.

There were two case-control studies in which exposure to paint and benzene seemed to increase the risk of aplastic anemia. In Bangkok, there were few exposures to benzene. There were significant associations for glues and thinners. The overall etiologic fraction for solvent exposure was 13%. There was no association in Khonkaen and Songkla.

## 3. Socioeconomic status

There was significant trends of increasing risk with decreasing years of education and total household income<sup>[9]</sup>. Low socioeconomic status is not a cause of aplastic anemia but rather a surrogate indicator of environmental risk factors possibly infectious agents, and toxic exposures that are prevalent in poor individuals.

## 4. Viral hepatitis

More than 200 cases have been described in which viral hepatitis was associated and in which no potentially myelosuppressive agents were involved. The disease typically occurs about two months after the onset of hepatitis, often while the hepatitis is improving or when it has resolved. Most cases were caused by non A non B hepatitis, but not hepatitis C. Sporadic cases of aplastic anemia associated with hepatitis A or B have also been reported.

As hepatitis is common in Thailand and aplastic anemia is more common there than in the West, we examined the possible association of hepatitis and aplastic anemia. There was no evidence of association of aplastic anemia with hepatitis B or hepatitis C. Previous exposure to hepatitis A as determined by immunoglobulin G seropositivity was significantly associated with aplastic anemia. However, no patients showed evidence of recent infection<sup>[10]</sup>.

Hepatitis A is not the cause of aplastic anemia because the prevalent rate in controls was so high (81%) but may be a surrogate marker for unknown risk factors in aplastic anemia that are transmitted under similar conditions. Hepatitis A is usually transmitted by an oral-fecal route, and the associated risk factor may be an enteric infectious agent.

## Conclusion

There have been few epidemiologic studies of aplastic anemia conducted to determine the incidence and possible etiologic factors. The incidence is higher in the Orient compared to the West. The incidence in Bangkok is twice higher than those reported by the IAAAS. The geographic differences among the regions may relate to different distributions of risk factors. There was an increase in the incidence with increasing age. In Bangkok, the double peak incidence is unusual; the incidence among young people suggests the possibility of occupational and environmental exposures as the risk factors.

Aplastic anemia is considered to be of unknown etiology. Drugs including penicillamine, gold, carbamazepine and non-steroidal anti-inflammatory drugs are reported to be associated with the disease, but a relatively low drug relationship was observed in Bangkok. A strong inverse association with socioeconomic status, an association with agricultural pesticide exposure, and a positive association with hepatitis seropositivity were described.

## References

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