Congenital Hypoplastic Thrombocytopenia with Skeletal Deformities in Siblings

By Sidney Shaw and R. A. M. Oliver

Hauser described a case of primary congenital aplasia of megakaryocytes with other congenital deformities. Several other instances of a similar condition associated with absent radii have recently been reviewed by Emery, Gordon, Rendle-Short, Varadi and Warrack. Gross, Groh and Weippl have described four cases of congenital hypoplastic thrombocytopenia with absence of both radii; two of these were siblings.

We record here a further instance of congenital hypoplastic thrombocytopenia with absence of both radii occurring in siblings.

Case 1: a female born at full term in April 1955, weighing 6 lb., 2 oz. The pregnancy was normal except for slight vaginal bleeding in the 12th week. This was the second pregnancy; the first had miscarried at two months.

The parents were in good health and there was no consanguinity. A maternal blood count was normal, with a normal platelet count. The mother's Wassermann reaction was negative and blood group B rhesus positive (to anti D).

The child was born with a deformity of both arms, due to the absence of both radii, but appeared otherwise healthy.

Melena occurred at the 6th week and was immediately followed by scattered petechiae in the skin and in the mouth, and by pallor. The infant was admitted to the hospital on June 11, 1955 and at that time weighed 7 lb., 7 oz. and was normally nourished; the liver was palpable and the spleen could be felt 2 cm. below the costal margin. There was no enlargement of lymph nodes.

Investigation showed a hemoglobin of 5 Gm.+%; the red cells showed frequent polychromatic forms and normoblasts. The total white cells were 63,000 cu.mm., with the differential count—blast cells 2.5%, promyelocytes 5%, myelocytes 30%, metamyelocytes 7%, neutrophils 34.5%, lymphocytes 14%, monocytes 6.5%, plasma cells 0.5%. Subsequent white cell counts varied between 15,800 and 131,000/cu.mm., and after the first differential count the incidence of early granular cells decreased, but there were usually 3 to 4% myelocytes. The platelet count was 2,600/cu.mm. The bleeding time was in excess of one hour. Coagulation time, clot retraction and prothrombin time were all normal. The Hess test was positive. Tibial marrow examination showed normoblastic hyperplasia, active leukopoiesis and a complete absence of megakaryocytes. Three subsequent marrow examinations confirmed the anmegakaryocytopoiesis. The Wassermann reaction was negative. Serum bilirubin was normal. Blood group B and rhesus positive (to anti D).

Treatment was by platelet transfusions, using silicone-coated apparatus and oral cortisone, 7.5 mg. increasing to 24 mg. daily. Splenectomy was carried out on October 26, 1955, but with temporary benefit only. The spleen weighed 21 Gm. and sections showed abundant splenic follicles with simple pulp hyperplasia; there was no evidence of leukemia.

The infant died on December 2 from cerebral hemorrhage. At necropsy there were also small hemorrhages in the lungs and myocardium; extramedullary hemopoiesis was...
found in the liver and lymph nodes. No megakaryocytes were seen in films or sections of the marrow.

Case 2: a male born at full term on June 6, 1957, weighing 6 lb., 7 oz. The pregnancy was normal. In addition to bilateral absence of both radii and ulnae there was cervical spina bifida and bilateral talipes equino varus.

Melena and skin petechiae occurred about the fourth week, but the child had gained weight normally and appeared well nourished; the spleen was palpable.

Investigation showed a hemoglobin of 3.3 Gm.%, a total white cell count of 17,000/cu.mm. and the differential count—neutrophils 36, lymphocytes 58, monocytes 6%. The platelet count was 40,000/cu.mm. Blood group B, rhesus test positive (to anti D). Tibial marrow was examined on August 19, 1957, and showed some erythroid hyperplasia; leukopoiesis was normal apart from eosinophilia (8% eosinophil myelocytes). No megakaryocytes were seen but a few giant platelets were present. At the same time the white cell count was 25,000/cu.mm., the differential count—blast cells 1, myelocytes 12, metamyelocytes 6, neutrophils 17, eosinophils 6, basophils 2, lymphocytes 51, monocytes 5%. There were a few normoblasts in the film. The platelet count 40,000/cu.mm.

On other occasions the white count had risen to 50,000/cu.mm. and the platelets to 70,000/cu.mm.

In November 1957 the petechiae increased in number, especially over the back. All forms of treatment had been refused by the mother, but permission was obtained for one transfusion and 150 cc. of blood was given on November 22, 1957; after that the hemoglobin rose to 13.4 Gm.%.

No other transfusions have been given and the hemoglobin level has been maintained; the infant continues to gain weight normally. The hemoglobin on discharge in April of this year was 13.6 Gm.% and the platelets had risen to 105,000/cu.mm.

**DISCUSSION**

The coincidence of absence of megakaryocytes and absence of the radii can best be explained on developmental grounds. It is between the sixth and eighth weeks of intrauterine life that the radii begin to develop, and at about this time platelet production is also thought to begin (Fruhling, Roger and Jobard).

Defects at this period of intrauterine life could be ascribed either to an environmental cause or a genetic abnormality. In our first case (Bell, Mold, Oliver and Shaw) there was an antenatal history of threatened abortion at the twelfth week, so that an environmental etiology could not be excluded. However, this abnormality in the pregnancy probably occurred too late to have been associated with these congenital defects; moreover, in the second infant there was no abnormality in the pregnancy at any time.

The occurrence of these rare disorders in siblings has also been recorded by Gross, Groh and Weippl and we consider this as good evidence in favor of a genetic cause.

Fanconi and others have described the association between skeletal defects and blood dyscrasia; there is usually aplasia involving the erythron predominantly, but thrombocytopenia with diminution in the number of marrow megakaryocytes has been frequently described (Estren, Suess and Dame shek). However, in Fanconi's syndrome the blood changes are not usually seen in infants.

The interesting association of Fanconi's anemia in one sibling and acute leukemia with similar skeletal deformities in another, has been recorded by Cowdell, Phizackerley and Pyke.
Emery et al.³ consider that these cases are related to congenital leukemia. In both of our patients there were leukemoid blood pictures on occasions as seen by the high white cell counts and the incidence of primitive cells in the peripheral blood. Hemopoiesis in the liver and lymph nodes in our first patient simulated leukemic infiltration, but these changes appeared to us to be those of extramedullary hemopoiesis in response to repeated hemorrhage.

The condition described in the two pairs of siblings by ourselves and Gross et al.⁷ differ from the cases of Fanconi’s syndrome in that the condition arises in the first few months of life and affects the megakaryocytes predominantly without hypoplasia of the erythron. We consider that these four patients represent variants of this syndrome.

**SUMMARY**

The occurrence of congenital hypoplastic thrombocytopenia with absent radii is described in siblings.
CONGENITAL HYPOPLASTIC THROMBOCYTOPENIA

Both presented with hemorrhagic manifestations within a few weeks of birth and the first died at the age of six and a half months. Reference is made to two other examples in siblings. These abnormalities are considered as due to a genetic defect and the cases are probably variants of Fanconi's syndrome.

SUMMARIO IN INTERLINGUA


REFERENCES

Congenital Hypoplastic Thrombocytopenia with Skeletal Deformities in Siblings

SIDNEY SHAW and R. A. M. OLIVER