Multiple Hemangiomata Associated with Thrombocytopenia: Remarks on the Pathogenesis of the Thrombocytopenia in this Syndrome

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THE ASSOCIATION of giant hemangiomata with thrombocytopenia was first described in 1940.[1] Up to the present time, 13 cases, all infants, have been reported in the literature.[2-10]

The purpose of this communication is threefold. First, we wish to describe the clinical features of a 13-year-old girl with multiple and extensive hemangiomata. Second, we shall present additional evidence to support the idea that the tumor plays a role in the pathogenesis of the thrombocytopenia. Third, we shall indicate that there is a certain risk in surgical removal of the hemangiomata.

Methods

The following clinical pathologic procedures were used: platelet count, Lempert-Kristensen[11]; bleeding time, Dacie[12]; clotting time, Lee and White[13]; plasma prothrombin time, Quick[14]; prothrombin consumption, Quick[14]; circulating anticoagulants, Singer[15]; determination of prothrombin and Factors V and VII (qualitative), Biggs and MacFarlane[16]; fibrinogen.[17]

Fibrinolysis was estimated by putting 5 ml. of whole blood into a sterile test tube and looking for evidence of gross lysis after the tube had been kept for 24 hours in a 37 C. water bath. In the thromboplastin generation test the standard technic of Biggs and Douglas[18] was used except that 1% Sequestrene in 0.7% saline was substituted for the 3.8% citrate which produced a more homogeneous platelet preparation. All platelet suspensions used in the thromboplastin generation tests were adjusted to 500,000 platelets per cu.mm.

Case Report

The patient, a 13-year-old girl, was admitted to our hospital on the 13th of August, 1957, for surgical removal of a painful hemangioma of the left labium of the vulva. She was the third child of a family in which both parents and two older sisters were apparently normal. At birth, multiple hemangiomata were observed over the right upper and left lower extremities as well as over the right upper back, left lower abdomen and vulva.

At the age of one year, the patient received three x-ray treatments of unknown dosage to a hemangioma of the right hand without any effect on its size. At the age of six years, small hemangiomata of the right arm were excised. There was no excessive bleeding following surgery. However, the patient noticed that after each operation another tumor appeared in the vicinity of the one excised. One month prior to admission, a tooth was extracted and the patient bled for four days, but did not require any transfusions.

On admission, the significant physical findings were the multiple hemangiomata distributed as shown in figure 1. Preoperative laboratory examinations revealed normal blood counts, bleeding and clotting times and normal routine blood chemistries. No platelet counts were available at this time. Skeletal survey did not reveal any hemangiomata in the bones. Electroencephalogram was normal.

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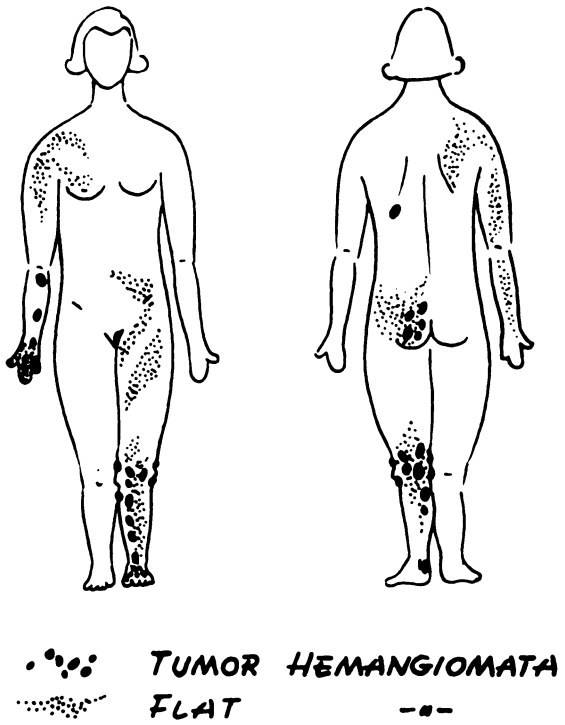

FIG. 1.—The distribution of the hemangiomata.

At operation a 1.5 cm. cavernous hemangioma of the left labium major was excised. After the operation there was some oozing from the wound which increased on the 10th post-operative day to a degree necessitating a blood transfusion. It was at this time that thrombocytopenia was first detected with a platelet count of 18,000/cu.mm. On the 28th of August (14th postoperative day) the patient was transferred to the medical ward where she continued to bleed profusely. Platelet counts, prothrombin times and fibrinogen levels, from that date, are presented in figure 2. Although a marked thrombocytopenia persisted throughout most of the course the bleeding time was always normal. The morphology of the platelets appeared normal on stained smears, and clot retraction was normal. Other findings that continued unchanged included a normal clotting time with a mild prolongation of the plasma prothrombin time due to a decrease in prothrombin and Factor VII, but normal Factor V. The serum prothrombin time was always abnormal. Platelet fragility, performed on two occasions, was decreased.*

Despite several wound revisions bleeding continued and an anemia developed characterized by a hemoglobin of 6 Gm.%. Fifty pints of blood, given over a two-week period, just maintained the hemoglobin at 10 Gm.%. No wound healing was evident. On the 6th of September (23rd postoperative day) the patient had more profuse wound bleeding than at any time previously. Additional coagulation studies at this time showed a clot lysis time of about two minutes and marked fibrinogenopenia (fig. 2). No circulating anticoagulant was detected. At this time the patient developed fever up to 40 C., and blood cultures yielded Staphylococcus aureus and Bacillus proteus, both sensitive to chloromycetin, Sigmamycin, novobiocyn and Furadantin. Intravenous achromycin was replaced by Sigmamycin, erythromycin and Furadantin. The patient's condition was

*We are indebted to Prof. Gurevitch of the Hadassah University Hospital, Jerusalem, for performing these tests.

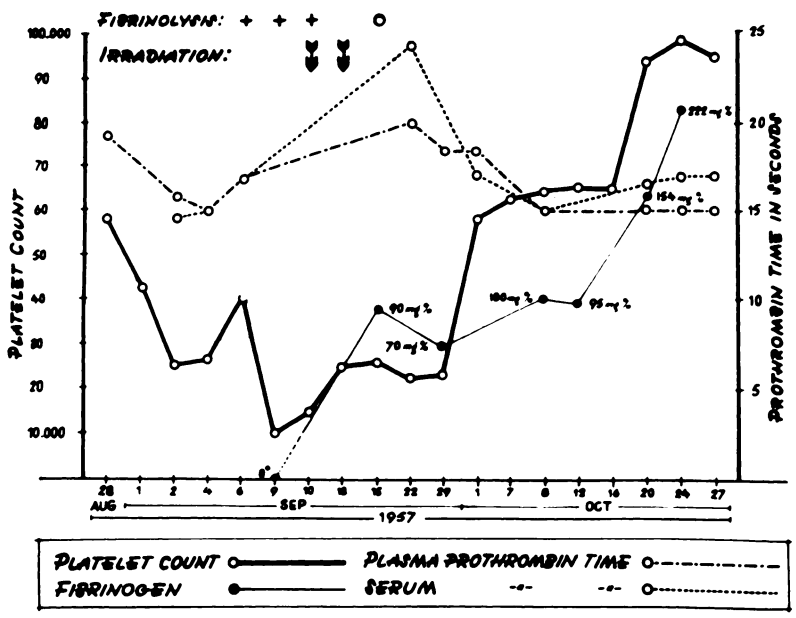

FIG. 2.—Postoperative platelet counts, prothrombin times and fibrinogen levels. The abnormal hemostatic tests after the operation.

critical. She continued to bleed profusely in spite of frequent transfusions of fresh blood, 12 Gm. of fibrinogen given intravenously, and vitamin K injections. In an effort to decrease the hemangiomata and thus possibly decrease the blood supply to the bleeding region, x-ray treatment of the adjacent abdominal hemangiomata was started. After the second 250 r (skin dose) treatment, areas of inflammation in the hemangiomata of the abdomen, the leg and the right upper back appeared. In some, thrombosis appeared; others fluctuated and ruptured. Cultures from the latter yielded Staphylococcus aureus and Bacillus proteus. This septic thrombophlebitis spread over the entire lower abdomen and left leg, continued for two weeks and gradually subsided. There followed a considerable decrease in the size of the tumors.

Two points are of particular interest. First, as the thrombophlebitis spread, the bleeding stopped, the wound started to heal rapidly, the temperature gradually returned to normal and repeated blood cultures were sterile. Second, with the shrinkage of the tumors the platelet count rose and remained at about 125,000 per cu.mm., although the prothrombin consumption and platelet fragility remained abnormal. Liver function tests, performed because of the persistently abnormal plasma prothrombin time and low fibrinogen level, showed a thymol turbidity of 8 units, a thymol flocculation of +++, a total protein of 8.3 Gm.% with 4.4 Gm.% of albumin.

One month after recovery the patient received therapeutic irradiation over the right hand and left foot. Except for a slight erythema there was no local reaction. This observation suggests that the thrombophlebitis was secondary to the septicemia and not to the x-ray treatment.

At the time of this report the patient is well, and all the hemangiomata, except those on the right arm, have diminished in size.

DISCUSSION

The patient described demonstrates an apparently intimate relation between hemangiomata and thrombocytopenia. The role of these tumors in the etiology of thrombocytopenia has been previously emphasized.[1-10] Good

and his collaborators[8] saw what appeared to be large numbers of platelets in biopsies of those tumors and concluded that the hemangiomata act as reservoirs of platelets. By performing platelet counts on both peripheral and hemangioma blood, we also demonstrated a higher platelet count in the latter (table 1). It is not yet clear whether the blood vessels in a hemangioma are abnormal and cause agglutination of platelets, or whether, as a result of stagnation in the tortuous hemangioma vessels, the platelets are damaged and therefore disintegrate faster. Both factors could be operative. Whatever the mechanism of the thrombocytopenia may be, it seems clear that after the hemangiomata shrink, the thrombocytopenia disappears.

When the peripheral platelet count in our patient approached the normal range, prothrombin consumption still remained abnormal. The thromboplastin generation test using the patient's serum, $BaSO_4$ plasma, platelets and *substrate* plasma was normal. This finding was surprising since in mild clotting abnormalities the thromboplastin generation test is usually more sensitive than the prothrombin consumption test. Because we were not able to demonstrate a circulating anticoagulant we felt that this unusual finding could be the result of a qualitative platelet deficiency. Support for this suggestion is presented in the results of table 2 which show that it was necessary to add three times as many patient's platelets as normal platelets in order to rectify the patient's prothrombin consumption.

This effect of washed platelets was surprising because when the patient's platelet count rose to 125,000 per cu.mm., the prothrombin consumption stayed abnormal. Prof. Gurevitch found a marked decrease in the fragility of the patient's platelets, which could possibly explain the normal thromboplastin generation test. It is conceivable that during washing the platelets are partially disrupted and the thromboplastic factor is released. If this is so, it is the first instance where a decreased platelet fragility and a concomitant abnormal prothrombin consumption have been demonstrated. Therefore, it is not clear if this patient belongs to the group of thromboasthenias of Braunsteiner.[19] It is of interest that other platelet functions, such as those concerned with bleeding time, clot retraction and platelet clumping, were normal.

The possibility that the abnormal prothrombin consumption was the result of a weak anticoagulant cannot be excluded in spite of our inability to

TABLE 1.—*Platelet Counts and Serum Prothrombin Time of Tumor-Blood and Peripheral Blood*

	Peripheral Blood		*Tumor Blood*	
Date	Platelet count/cu.mm.	Serum Prothrombin time (in sec.)	Platelet count/cu.mm.	Serum Prothrombin* time (in sec.)
10/7	62,000	16	114,000	35
10/10	64,000	17	122,000	22
10/15	65,000	15	124,000	17
10/20	103,000	16	97,000	16.5
10/23	98,000	16.5	104,000	16
10/27	95,000	17	93,000	15

*Normal serum prothrombin time over 20".

TABLE 2.—*The Effect of Different Concentrations of Patient's and Normal Platelets on the Prothrombin Consumption of Patient's Blood*

Patient's* Blood in ml.	Saline (ml.)	Platelets/cu.mm. added 0.2 ml.		Serum† Prothrombin Time (in sec.)
		Normal	Patient	
1.8	0.2	—	—	15
1.8	—	60,000	—	25
1.8	—	—	60,000	17
1.8	—	120,000	—	42
1.8	—	—	120,000	19
1.8	—	—	180,000	24.5

*Having a platelet count of 96,000 per cu. mm.

†Plasma prothrombin time performed simultaneously was 15 seconds.

demonstrate it. However, we do feel that the normal thromboplastin generation using the patient's $BaSO_4$ plasma and serum excludes AHF, PTC and PTA deficiencies of sufficient severity to produce this abnormal prothrombin consumption. Furthermore, our patient's plasma has corrected the clotting time and the prothrombin consumption of a hemophiliac blood, although we could not perform such experiments with PTC or PTA deficient bloods since such patients were not available.

Finally, to our knowledge, our patient is the only individual who has reached the age of 13 with such extensive hemangiomata. All previous cases have been in infants.

SUMMARY AND CONCLUSIONS

1. A 13-year-old girl with multiple hemangiomata and thrombocytopenia is described.

2. Complications of surgical treatment included severe bleeding, septicemia and a fibrinolytic event.

3. Simultaneous platelet counts from the tumor and peripheral blood were performed and showed a significantly higher concentration of platelets in the tumor vessels.

4. With the rise in the platelet count, a decreased platelet fragility as well as a persistently abnormal prothrombin consumption could be demonstrated.

5. The possible role of the tumor in the pathogenesis of the thrombocytopenia is discussed.

SUMMARIO IN INTERLINGUA

1. Es describite le caso de un puera de 13 annos de etate con hemangiomas multiple e thrombocytopenia.

2. Le complicationes del tractamento chirurgic includeva sever grados de sanguination, septicemia, e un evento fibrinolytic.

3. Simultanee numerationes plachettal esseva effectuate in le tumor e in sanguine peripheric. Esseva constatate un significativemente plus alte concentration de plachettas in le vasos tumoral.

4. In association con le augmento del numeration de plachettas il esseva possibile monstrar un reducite fragilitate plachettal e etiam un persistente anormalitate in le consumption de prothrombina.

5. Le rolo possibile del tumor in le pathogenese del thrombocytopenia es discutite.

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