THROMBOPENIC PURPURA

Parathyroid Hormone in the Treatment of a Case

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IN 1932 Lowenburg and Ginsburg[1] first reported an apparent beneficial result following the accidental administration of parathyroid hormone to a young patient with essential thrombocytopenic purpura. The dosage was sufficient to cause severe hypercalcemia and clinical signs of toxic overdosage. Again in 1936 these authors[2] obtained a similar clinical response following the subcutaneous administration of 60 units of parathyroid hormone daily for four consecutive days. Both patients had failed to respond to other measures such as transfusions and antivenin injections. In neither patient had splenectomy been performed prior to the administration of parathyroid extract.

Parathyroid hormone has been used at the Cleveland Clinic since 1940 as one of the methods of treatment in patients with thrombopenic purpura. This report concerns the first patient treated at the Clinic by the induction of hypercalcemia with parathyroid hormone. The patient reported here had failed to respond to all the usual methods of therapy including splenectomy.

Case Report

A 26-year-old housewife was admitted to the Cleveland Clinic Hospital on July 14, 1940, with complaints of excessive menstrual bleeding, profuse epistaxis, and bruising easily with slight injury. In February, 1940 she first noticed "black and blue" spots under the skin and several weeks later menorrhagia persisting for ten to fourteen days. In May, 1940 she developed prolonged and recurrent nasal and gingival bleeding which remained uncontrolled despite local measures of treatment.

The past history and family history contributed nothing pertinent. The menstrual cycles were normal prior to her present illness and she had never been pregnant. The patient had been hospitalized at home with a tentative diagnosis of idiopathic thrombopenic purpura and had failed to respond to liver extract, oral iron, intravenous calcium, snake venom (moccasin), or multiple transfusions. On detailed inquiry, she denied the ingestion of any drugs known to cause purpura preceding her illness.

Physical examination revealed an acutely ill young woman with moderate pallor and diffuse purpuric lesions of the skin and oral mucosa. Crusts of dried blood were evident in the nares and gingival bleeding was pronounced. The gums showed no hypertrophy. The thyroid was not enlarged nor was there generalized lymphadenopathy. Examination of the chest revealed the lung fields to be clear. The heart was not enlarged and the heart rate was 110 beats per minute with an audible soft apical systolic murmur. The abdominal examination revealed no abnormalities, the liver and spleen were not palpable. The remainder of the physical examination, including the pelvis and rectum did not reveal any abnormalities.

On admission her oral temperature was 101 degrees, pulse 110, blood pressure 118/70. The patient remained febrile, with the temperature fluctuating daily from 101 to 102 F. for the first sixty-five hospital days.

The red blood cell count was 1,450,000; hemoglobin 4.8 Gm. (Haden-Hauser), or 31 per cent of normal; white blood cells 6150 with 73 per cent neutrophilic leukocytes, 16 per cent

lymphocytes, 4 per cent eosinophils, and 7 per cent monocytes. The reticulocyte count was 31 per cent. The blood smear showed severe anisocytosis and poikilocytosis. No immature white blood cells were seen. The platelet count was 10,000 per cu. mm. by the Rees-Ecker method. Bleeding time was longer than one hour with no clot retraction in twenty hours. The coagulation time was twelve minutes by the Lee-White technic. Study of bone marrow smears obtained by sternal puncture revealed definite stimulation of erythropoesis, normal distribution of the myeloid cells, and an increase of megakaryocytes. The urinalysis was normal and the blood Wassermann and Kahn reactions were negative.

The patient was given several blood transfusions and splenectomy was performed by Dr. Robert Dinsmore on July 16. The immediate postoperative course was stormy with development of an atelectasis of the right lower lobe, persistence of low-grade fever, and failure of an increase of blood platelets. The platelet count remained between 10,000 and 20,000 for thirty consecutive postoperative days in spite of transfusions, calcium gluconate intravenously, and large doses of vitamin C. The epistaxis, gingival bleeding, and oozing about the incision continued. Two courses of "Koagamin" were given without benefit.

On August 14, the thirtieth postoperative day, parathormone administration was begun. At this time the base-line studies revealed the platelet count to be 10,000, blood calcium 9.2 mg. per 100 cc., and blood phosphorus 3.4 mg. per 100 cc. The patient received 150 units of parathyroid hormone (Lilly) intramuscularly the same day; 450 units on August 15, and 350 units on August 16 in divided doses every six to eight hours (figs. 1 and 2). On the date of the last administration, the gingival, nasal, and vaginal bleeding ceased, the platelet count rose abruptly to 120,000, and the blood calcium reached a peak of 13.9 mg. per 100 cc. During the three days of parathormone therapy, the patient was given daily intravenous injections of 10 cc. of 10 per cent calcium gluconate.

With the cessation of bleeding, the clinical course steadily improved despite the development of an intra-abdominal abscess which necessitated incision and drainage on September 30. Re-check study of the bone marrow by sternal puncture on August 29 revealed a diminution in the number of megakaryocytes with moderate hyperplasia of the erythroid and myeloid cells. The megakaryocytes appeared larger and more mature.

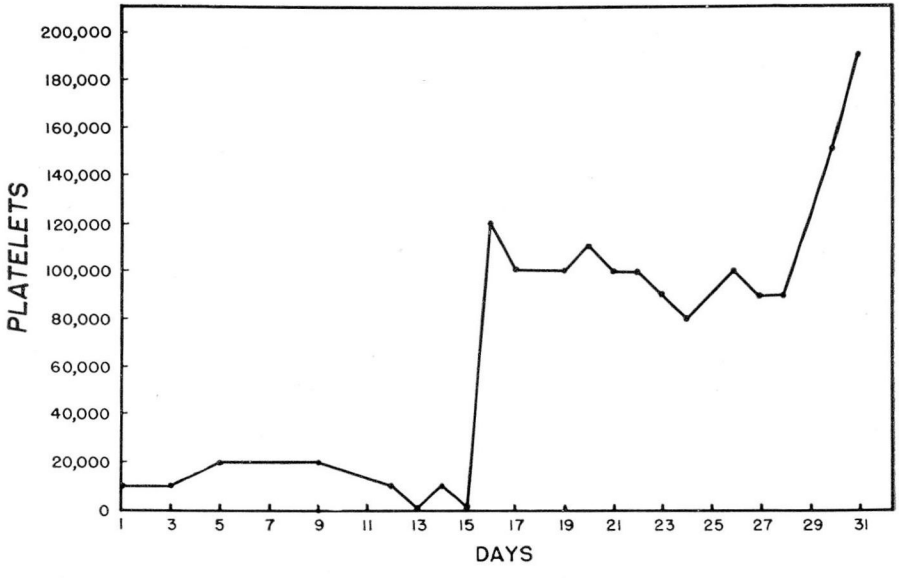

FIG. 1

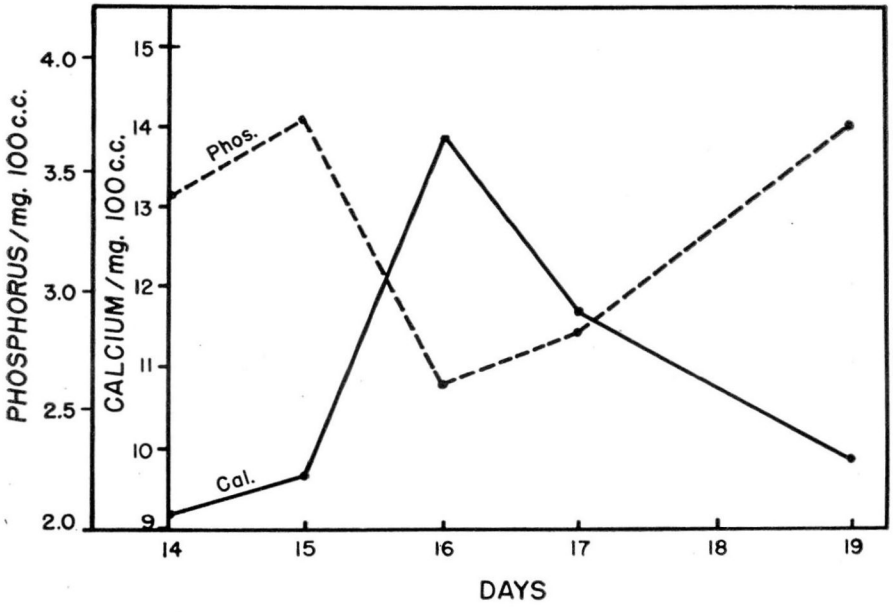

FIG. 2

The patient was discharged on September 28, 1940 at which time the blood studies were normal except for a moderate hypochromic anemia. The patient was last seen in August, 1948 and she stated that she had been entirely well since discharge and had had normal menstrual periods. No abnormalities could be found on physical examination, and the tourniquet test was normal. The complete blood count with hemorrhagic studies was also normal and the platelet count was 330,000 per cu. mm.

Discussion

The mechanism of the bleeding tendency in thrombopenic purpura is obscure. The number of circulating platelets is an important diagnostic feature in such patients, but the cause of the diminution in their numbers remains debatable. As the bone marrow studies usually reveal a normal or increased number of megakaryocytes, it has been suggested that the platelet deficiency is due to a maturation arrest of the megakaryocytes. Others believe that the circulating platelets are reduced because of excessive phagocytic activity of the spleen in this type of purpura. The exact role of capillary fragility with adherence of platelets to injured or diseased endothelium of the capillaries is not clear. It appears, however, to be a definite factor in many such patients.

With the production of hypercalcemia by parathyroid hormone, there has been an apparently dramatic increase of circulating platelets, decrease in bleeding time, and clinical improvement in a number of patients. This response appears to be due to the hypercalcemia, the latter representing an increase in the ionized fraction of the blood calcium. No quantitative relationship between

the level of the blood calcium and the number of circulating platelets has been demonstrated. In those patients in whom the administration of parathormone failed to cause a demonstrable hypercalcemia, the results have been equivocal or poor. Mathewson and Cameron[3] reported the occurrence of apparent parathormone inactivity in a patient given 300 units subcutaneously in divided doses at four day intervals with no increase in the blood calcium. Similar results in several patients to whom much larger quantities of the hormone were given have been observed here, but no satisfactory explanation of such apparent inactivity can be offered.

With few exceptions, including the patient reported, this method of treatment in essential thrombocytopenic purpura has been used prior to splenectomy. In those patients who failed to obtain a satisfactory clinical and hematological response to induced hypercalcemia, splenectomy was generally advised. Following splenectomy, these patients rarely failed to obtain a satisfactory response. Rosenthal[4] reported in 1937 the use of parathormone in the treatment of 7 patients with essential thrombocytopenic purpura. Five were chronic cases and 2 were acute. He stated that no beneficial results were obtained. The details of dosage of parathyroid hormone and blood calcium levels were omitted.

Technic

Prior to the administration of parathyroid hormone, the diagnosis of idiopathic thrombopenic purpura must be established beyond any reasonable doubt, and it is advisable that the patient be hospitalized. Following withdrawal of blood for platelet, calcium, and phosphorus examinations, the patient is given 100 to 200 units (1 to 2 cc.) of parathyroid hormone* intramuscularly. The blood calcium and phosphorus level is checked daily along with the platelet count. Subsequent doses are adjusted, depending on the clinical evidence of toxic effects of hypercalcemia, and on the blood calcium level. In children 100 to 200 units daily usually produce a significant hypercalcemia in 48 hours. In adults it is frequently necessary to give 200 units every six hours for three or four consecutive days, discounting the drug when a blood calcium level of 15 mg. per 100 cc. is reached. In the first group of patients treated, 10 cc. of 10 per cent calcium gluconate was given intravenously once or twice daily, to counteract, if possible, the rapid withdrawal of calcium from the bones. Additional calcium, either orally or parenterally, has not been used routinely in subsequent cases.

The toxic effects of acute hypercalcemia primarily consist of nausea, vomiting, and diffuse abdominal crampy pain, and they generally do not occur unless the blood calcium is above 15 mg. per 100 cc. The physiologic action of parathormone is not greater than twenty-four hours, and toxic effects subside rapidly upon cessation of the drug.

To date there is general agreement that the two procedures most likely to produce beneficial results are repeated blood transfusions and splenectomy.

*Lilly's.

There is little doubt that transfusions afford only temporary improvement. The results of splenectomy have stood the test of time, but it is recognized that all failures are not due to the presence of accessory spleens overlooked at the surgical procedure.

The clinical course of this disease is so variable, with relapses, unpredictable recovery, and inconstant severity, that the evaluation of any single form of treatment is difficult. It can be stated, however, that inducing acute hypercalcemia with parathyroid extract has apparently produced a satisfactory response in several patients with thrombopenic purpura and is worthy of further investigation.

Summary

A patient apparently recovered from thrombopenic purpura as a result of the induction of acute hypercalcemia with parathyroid hormone. Splenectomy performed thirty days prior to this treatment had been of no demonstrable value.

References

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3. Mathewson, F. A. L., and Cameron, A. T.: An apparent instance of parathormone inactivity. Canad. M. A. J., **36**:141-148 (Feb.) 1937.
4. Rosenthal, N.: Course and treatment of thrombocytopenic purpura. J.A.M.A. **112**:101-106 (Jan. 14) 1939.