colleagues at this unit for their helpful comments. We are also indebted to Mr. A. W. Hyett for supervising the apparatus during the tests and to Miss A. M. Dawkins and Mr. K. Houston for technical assistance.

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Platelet Life-span and Sites of Platelet Sequestration in Onyalai*

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British Medical Journal, 1969, 4, 146–148

Summary: With radioactive chromium, platelet kinetic studies were carried out in four patients with onyalai, a form of thrombocytopenic purpura occurring in the African Negro. Results were compared with those of White patients suffering from idiopathic thrombocytopenic purpura. In the onyalai patients platelet life-span was considerably reduced, and this was associated with a definite rise in radioactivity over the spleen in three of the four cases. In two patients remission was associated with steroid therapy, while in the other two remission followed splenectomy after steroids had failed to raise the platelet count. These findings are similar to those in White patients with idiopathic thrombocytopenic purpura.

Introduction

Onyalai is a Bantu name for a bleeding disease characterized by the presence of blood blisters in the mouth (Wellman, 1904). The condition, which is widespread in the Bantu throughout Africa south of the Sahara, is a form of thrombocytopenic purpura (Blackie, 1937) in which megakaryocytes are present in the bone marrow in normal or increased numbers (Gear, 1938; Lewis and Lurie, 1953). Most cases run an acute course indistinguishable from acute idiopathic thrombocytopenic purpura in Whites (Metz *et al.*, 1958). The relation between onyalai and other forms of idiopathic thrombocytopenic purpura is debatable. The introduction of radioisotopic methods of measuring platelet life-span and determining the sites of platelet sequestration has enabled idiopathic thrombocytopenic purpura to be classed as a form of thrombocytopenia resulting from increased peripheral destruction of platelets (Hirsch and Gardner, 1952). As the mechanism of the thrombocytopenia in onyalai is unknown, platelet life-span and sites of platelet destruction were studied in Bantu patients with onyalai, and the results compared with those of White patients with idiopathic thrombocytopenic purpura. Considerable shortening of platelet life-span was found in all the onyalai patients, but there was no consistent pattern of surface radioactivity.

* This work was supported by a research grant from the Atomic Energy Board, Pretoria.

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Material

Seven patients were studied. Four were typical cases of onyalai—that is, Bantu with haemorrhagic bullae in the mouth, thrombocytopenic purpura, and a normal or an increased number of megakaryocytes in the marrow. The relevant clinical and haematological data are summarized in Table I. The other three were white patients with acute thrombocytopenic purpura associated with normal or increased number of megakaryocytes in the marrow. No lupus erythematosus cells were detected in any of the patients studied.

Methods

Platelet survival was measured with radiochromium (^{51}Cr) as described by Harker (1968). Autologous or ABO compatible blood was drawn into a Fenwall triple bag plasmapheresis set containing ACD (citric acid, trisodium citrate, and dextrose) solution, in a ratio of 7 to 1. The triple bag was centrifuged at 300 g. for 12 minutes, the platelet-rich plasma being transferred into a satellite bag. The red cells were reinfused into the donor. When necessary the pH of the platelet-rich plasma was adjusted to 6.5 with 0.15 M citric acid. The platelet-rich plasma was centrifuged at 1,000 g. for 16 minutes and most of the supernatant platelet-poor plasma transferred into the second satellite bag. The platelet button was resuspended in about 20 ml. of remaining plasma. Then 250 μCi of sodium chromate (^{51}Cr) solution B.P. (specific activity 50–150 mv./mg.), obtained from the Radiochemical Centre, Amersham, U.K., was added to the platelet suspension and incubated for 15 minutes. The labelled platelets were washed twice in platelet-poor plasma from the second satellite bag and then resuspended in from 15 to 20 ml. of plasma. An aliquot was removed for the preparation of a standard. All these manipulations were performed at room temperature and under sterile conditions.

The ^{51}Cr -tagged platelets (in about 20 ml. of plasma) were injected intravenously into the recipients, following which venous blood samples (10 ml.) were drawn into 0.2 ml. of 10% potassium edetic acid at 10-minute intervals for the first half-hour and then half-hourly for the next three hours, for the first day. Subsequently blood samples were drawn daily until the platelet radioactivity was less than 10% of the peak value. After the addition of 5 ml. of saline the blood samples were centrifuged at 300 g. for seven minutes and the platelet-rich plasma was removed. This procedure was repeated, and the platelet suspensions were pooled. The pooled platelet-rich plasma was then centrifuged at 1,500 g. for 20 minutes, the super-

TABLE I.—*Relevant Clinical and Haematological Data on Four Patients with Onyalai*

Case No.	Age	Sex	History	Physical Examination	Platelets/cu.mm.	Bone Marrow	Clinical Course
1	20	M	Bleeding from mouth. Epistaxis. Haematuria	Bullae in mouth. Purpura. No splenomegaly	10,000	Normal erythropoiesis and granulopoiesis. Numerous megakaryocytes. No "platelet budding"	No clinical or haematological response to prednisone 60 mg. daily for 6 weeks. Platelets 285,000/cu.mm. 6 weeks after splenectomy
2	24	M	Bleeding from mouth. Bruising	Bullae in mouth. Purpura. Echymoses. No splenomegaly	4,000	Normal erythropoiesis and granulopoiesis. Normal number of megakaryocytes but no "platelet budding"	No clinical or haematological response to prednisone 60 mg. daily for 8 weeks. Platelets 160,000/cu.mm. 6 weeks after splenectomy
3	22	F	Bleeding from mouth. Epistaxis. Haematuria. Melaena	Bullae in mouth. Purpura. Conjunctival haemorrhages. No splenomegaly	20,000	Normal erythropoiesis and granulopoiesis. Normal number of megakaryocytes but no "platelet budding"	Blood transfusion. Clinical and haematological response to prednisone 60 mg. daily. Platelets 180,000/cu.mm. 8 weeks after stopping prednisone therapy
4	26	F	Epistaxis	Bullae in mouth. Purpura. No splenomegaly	10,000	Normal erythropoiesis and granulopoiesis. Increased numbers of megakaryocytes but no "platelet budding"	Clinical and haematological response to prednisone 60 mg. daily. Platelets 220,000/cu.mm. 8 weeks after stopping prednisone therapy

nantant completely decanted, and 0.5 ml. of the saline added. The standard was prepared by adding 100 μ l. of tagged platelet suspension to 2 ml. of ammonium oxalate in duplicate. The mixture was centrifuged at 1,500 g. for 20 minutes and the supernatant decanted. The platelet button was covered by 0.5 ml. of saline. The ^{51}Cr radioactivity of the platelet buttons prepared from the blood samples and the standard were assayed in a gamma-scintillation counter. The radioactivity in platelets was plotted against time on arithmetic graph paper, and platelet life-span expressed as the time for the radioactivity to reach 10% of the initial value after mixing. In six normal subjects studied the platelet life-span was seven to nine days.

Concurrently with the measurement of platelet life-span, surface radioactivity over the spleen, liver, and heart was measured with a directional scintillation counter. Surface radioactivity readings were divided by the number of microcuries of platelet ^{51}Cr injected, and the results expressed as counts/sec./ μCi injected.

Results

Onyalai Patients

In three of the onyalai patients platelet survival studies were carried out, using healthy subjects as controls, in the following way: ABO compatible platelets were labelled with ^{51}Cr and divided into two aliquots. One aliquot was injected into the onyalai patient and the other into a healthy ABO compatible recipient. In the fourth patient the study was carried out in the same way, except that a suitable healthy control was not

available. The platelets disappeared from the circulation of the onyalai patients extremely rapidly, while in healthy recipients who received aliquots of the same labelled platelets platelet survival was normal (Table II). The surface counting

TABLE II.—*Life-span of ^{51}Cr -labelled ABO Compatible Normal Platelets Infused into Onyalai Patients and Healthy Controls. Aliquots of Same Labelled Platelets were Infused into Each Patient-Control Pair*

Case No.	Platelet Life-span	
	Onyalai Patient	Healthy Control
1	53 minutes	7 days
2	11 minutes	9 days
3	24 hours	8 days
4	18 minutes	—

patterns varied. In three patients (Cases 1, 2, and 3) radioactivity over the spleen was much greater than over the liver, while in Case 4 radioactivity over these two organs was about equal. These results are shown in the Chart.

Experiments with Onyalai Plasma.—Attempts were made to demonstrate a humoral thrombocytopenia-inducing factor in plasma from two of the onyalai patients. Plasma was drawn from these patients in a thrombocytopenic phase. Normal platelets were incubated in onyalai plasma at 37° C. for 30 minutes, following which the platelets were labelled with ^{51}Cr and transfused into normal ABO compatible volunteer recipients. Platelet life-span was 9 and 8½ days in the two recipients respectively. The results thus failed to show shortening of the survival of normal platelets following in-vitro incubation in onyalai plasma.

Platelet survival (top), surface counting (middle), and organ ratios (bottom) in four onyalai patients (Cases 1-4) after the infusion of ^{51}Cr -labelled normal platelets.

Idiopathic Thrombocytopenic Purpura Patients

Platelet survival studies were carried out in three White patients with idiopathic thrombocytopenic purpura. Platelet life-span was 34, 190, and 180 minutes respectively. Surface counting showed higher radioactivity over the spleen compared with the liver in two patients, while in the third the liver showed the greatest radioactivity.

Discussion

In-vitro labelling of platelets with radioactive sodium chromate is a valid technique for the determination of platelet life-span, which by this method ranges from 7 to 10 days in normal subjects, a value corresponding to that obtained with other radioisotopic methods (Baldini, 1966). In the present study platelet life-span in healthy subjects was seven to nine days.

In the four patients with onyalai the platelet life-span was greatly shortened in the thrombocytopenic phase when compared with normal healthy subjects who received aliquots of the same labelled platelets. These results and adequate megakaryocyte production in the bone marrow show the mechanism of the thrombocytopenia in onyalai to be peripheral destruction of platelets, and not the failure of megakaryopoiesis. This finding is similar to that described in patients with idiopathic thrombocytopenic purpura (Hirsch and Gardner, 1952) and confirmed in the White idiopathic thrombocytopenic purpura patients in the present study.

A thrombocytopenia-inducing factor has been demonstrated in the plasma of patients with idiopathic thrombocytopenic purpura. This was originally discovered in classical self-experimentation studies by Harrington *et al.* (1951), where infusion of plasma from patients with idiopathic thrombocytopenic purpura produced thrombocytopenia in normal subjects. In the present study attempts were made to demonstrate such a factor in the plasma of patients with onyalai. Previous incubation of normal platelets in onyalai plasma failed to reduce their life-span when subsequently infused into normal recipients. This does not exclude the presence of a humoral factor in the plasma of these patients, as the in-vitro conditions may not have been optimum for the action of such a factor. Ideally, to demonstrate such a factor the test plasma should be infused into control subjects, but such an experiment was thought to be too hazardous.

The surface radioactivity after infusion of labelled platelets to the onyalai patients was variable, though three of the four patients showed greater radioactivity over the spleen than over

the liver. In White patients with idiopathic thrombocytopenic purpura the findings are similar; decrease in platelet life-span is invariable, but there is no consistent surface counting pattern. Determination of sites of platelet sequestration does not correlate well with response to steroid therapy. In two of the onyalai patients high splenic radioactivity was associated with failure to respond to steroids, while a third patient with a similar surface counting pattern responded to this treatment. If a predominant splenic sequestration pattern is noted, however, splenectomy results in a good remission (Najean *et al.*, 1963). Lightly sensitized platelets are sequestered in the spleen, whereas heavily sensitized platelets are sequestered in the liver (Aster and Keene, 1969).

The similarity between onyalai and idiopathic thrombocytopenic purpura in Whites was recognized with the earliest description of the disease, and has been a cause for comment in many subsequent publications. The evidence that onyalai is a separate disease entity was reviewed by Metz and Kramer (1958), who concluded that the presence of haemorrhagic bullae in the mouth in thrombocytopenic states was independent of the cause of the thrombocytopenia, and therefore retention of the term onyalai as indicative of a separate disease entity was unwarranted. The results of the present study are compatible with this view. The mechanism of the thrombocytopenia in onyalai is similar to that of idiopathic thrombocytopenic purpura in Whites, as is the pattern of surface radioactivity after infusion of chromium-labelled platelets.

We wish to thank the Director, South African Institute for Medical Research, for facilities to carry out this study; Mr. D. Hart for technical assistance; and Dr. Fay Segal for referring one of the onyalai patients.

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Medical Memoranda**"Antimongolism" Syndrome**

British Medical Journal, 1969, **4**, 148-149

Not more than 10 cases of "antimongolism" syndrome have previously been reported, and its clinical and cytogenetic entity has not yet been established clearly enough. We have recently studied a case of partial monosomy G syndrome in a Japanese infant, to our knowledge the first case in the Orient.

CASE REPORT

The patient, a boy aged 4 years, was the first and only child of a 25-year-old mother and a 27-year-old father. He was born after

an uneventful full-term pregnancy and normal delivery. The birth weight was 2,430 g. There was no history of parental radiation exposure, viral infection, or drugs being taken during early pregnancy.

He had had a sporadic clonic seizure about once a month, lasting for 5 to 20 minutes, after which he would fall asleep and become febrile. He cannot speak, partly because of mental retardation and partly because of deformities of the oral cavity.

Examination showed him to be underdeveloped and mentally retarded (intelligence equivalent to about a 1-year-old). Bilateral cataract, broad nasal bridge, low-set external ears (Fig. 1), inguinal hernia, hypospadias, scrotal dysplasia, and clubfoot were observed. These are common stigmata which have been noted in other reported cases of the syndrome (Lejeune *et al.*, 1964; Cohen, 1966; Penrose, 1966; Reisman *et al.*, 1966; Thorburn and Johnson, 1966;