
The Use of Indium-111 Oxine Platelet Scintigraphy and Survival Studies in Pediatric Patients with Thrombocytopenia

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We have utilized ^{111}In -labeled heterologous platelets to investigate the mechanism of thrombocytopenia in ten children. From the scintigraphic findings, platelet survival times, and clinical information, thrombocytopenia was ascribed to decreased production or to increased destruction. Two patients were found to have bone marrow production defects. Two patients with hemangiomas were studied. In one, the hemangioma was shown not to be the cause of thrombocytopenia. In the second, the hemangioma was proven the source of platelet destruction, but was much more extensive than clinically evident. In both, surgical manipulation of the hemangioma was avoided. Six additional patients had thrombocytopenia due to accelerated destruction. In four, the spleen was shown responsible. In two, however, the spleen was shown not to be responsible for the low platelet counts, and splenectomy was avoided. Thus, ^{111}In -platelet scintigraphy and survival studies are valuable in the classification and management of childhood thrombocytopenia. We believe that this study should be performed, when possible, in any child with thrombocytopenia where the mechanism is unclear or the therapeutic intervention involves splenectomy or resection of a hemangioma.

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Thrombocytopenia can be caused by increased destruction, decreased production, or sequestration of platelets. To date, there have been few methods to accurately investigate platelet kinetics in children. The development of indium-111 (^{111}In) oxine-labeled platelets has provided an important tool for classifying the mechanism of thrombocytopenia and evaluating clinical interventions. This labeling technique has several advantages over the traditional chromium-51 (^{51}Cr) label. These include high labeling efficiency, thereby permitting small sample volumes, and medium-energy gamma rays that enable high quality organ imaging. We describe the use of this technique in children with thrombocytopenia and its impact upon the classification and management of this condition.

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MATERIALS AND METHODS

Patients

Ten children (ages 9 mo-16 yr) with thrombocytopenia, platelet count $< 150 \times 10^9/\text{l}$, in whom the etiology was unclear or splenectomy was proposed, were referred for platelet survival and scintigraphy studies. Clinical characteristics are outlined in Table 1.

Platelet Lifespan Studies

The method for performing [^{111}In]oxine platelet survivals has been reported in detail previously (1,2). Random, fresh, unrelated donor platelets (pooled from several donors, with the exception of Patient 9, whose mother's platelets were used), ABO compatible, HIV and hepatitis B surface antigen negative were centrifuged at $1000 \times g$ for 10 min. The platelet-poor plasma was decanted and saved. The platelet button was washed with acid citrate dextrose (ACD) and resuspended in 100-500 μCi of [^{111}In]oxine for 30 min at room temperature. The platelets were then recentrifuged and suspended in the platelet-poor plasma. Eight $\mu\text{Ci}/\text{kg}$, a maximum dose of 500 μCi , were injected through a peripheral intravenous line. (Patients 8 and 9 received 4 and 10 μCi , respectively) Blood sampling was performed [0.5-1.0 cc into ethylenediaminetet-

TABLE 1

Patient no.	Age (yr)	PLT Ct	Pre-study diagnosis	Survival time*	% Recovery	S/L (2.3-4.4)	S/H (2.9-6.3)	Findings	Diagnosis and outcome
				(Normal adult) (175-228)	(Normal adult) (55-72)				
1	13 yr	12×10 ⁹ /l	Congenital thrombocytopenia, ? splenic sequestration, bone marrow transplantation candidate	95 hours	82%	3.0	5.3	No evidence for sequestration; normal distribution (Fig. 1)	Congenital thrombocytopenia due to platelet production defect; splenectomy avoided
2	12 yr	15×10 ⁹ /l	Fanconi's Anemia; ? splenic sequestration, bone marrow transplantation candidate	136	62	2.3	2.8	No evidence for sequestration; normal distribution	Thrombocytopenia due to platelet production defect; splenectomy avoided and bone marrow transplantation performed
3	9 mo	5×10 ⁹ /l	Hemangioma	20	9	0.7	3.7	Extensive uptake in hemangioma and in unsuspected sites (Fig. 2)	Hemangioma was unresectable; medical therapy attempted
4	17 mo	23×10 ⁹ /l	Hemangioma	2	29	2.7	29	Hemangioma does not accumulate platelets (Fig. 3); there is marked uptake in the spleen and liver	Further evaluation showed that thrombocytopenia was due to immune mechanisms; thrombocytopenia resolved after treatment with i.v. IgG
5	16 yr	44×10 ⁹ /l	AML; poor response to platelet transfusions	38	46	4.0	7	Abnormal splenic uptake	Increased platelet destruction; AML; bone marrow transplantation, patient died 1 mo later
6	3 mo	50×10 ⁹ /l	Premature infant; consumptive thrombocytopenia	53	15	3.0	6	Marked accumulation of platelets in spleen	Multiple problems: respiratory distress; intraventricular hemorrhage; splenomegaly
7	3½ mo	2.7×10 ⁹ /l	ITP	1	20	3.0	29	Platelet destruction primarily in spleen with increased splenic uptake	ITP; however, no response to steroids or i.v. IgG
8	15 yr	1×10 ⁹ /l	ITP	0.3	24	5.9	20	Increased uptake in spleen (Fig. 4)	ITP; thrombocytopenia resolved after splenectomy
9	17 yr	3×10 ⁹ /l	ITP; S/P splenectomy; accessory spleen	1.4	19	0.04	1.0	Increased uptake in liver and lungs; accessory spleen accumulates only 2% of the injected activity (Fig. 5)	ITP; accessory spleen, splenectomy avoided
10	14 yr	4×10 ⁹ /l	Aortic insufficiency ? ITP	0.7	7	0.4	14.6	Spleen:liver ratio does not suggest splenectomy will be helpful (Fig. 6)	Aortic valve replaced; thrombocytopenia resolved on glucocorticoids; splenectomy avoided

S/L - spleen:liver ratio; S/H - spleen:heart; * Survival times and recovery rates are based on adults receiving autologous platelets (2).

raacetic acid (EDTA)] at 5 min, 1, 2, 3, 4, 6, 12, 24, 48, and 72 hr after injection.

Platelet recovery was calculated from the 5 min (when available) or 1 hr sample using the following equation and assuming a blood volume of 80 ml/kg:

$$\% \text{ recovery} = \frac{\text{cpm/ml} \times \text{total blood vol}}{\text{injected dose (in cpm)}}.$$

Radioactivity was measured in whole blood using a gamma scintillation well counter (1085 Nuclear Chicago Gamma Counter) and platelet survivals calculated from multiple models (2,3). For most patients with thrombocytopenia, the linear, logarithmic, and multiple hit models gave similar results.

Organ Imaging

Anterior and posterior whole-body images were obtained at 1 and 24 hr using a large field-of-view-gamma camera interfaced with a computer. Regions of interest were drawn around the heart, liver, spleen, whole body, and other areas if indicated, and the geometric means of the activity from each region were used to compare organ uptake of ^{111}In platelets. Spleen:heart and spleen:liver ratios were calculated from the 24-hr images to assess the reticuloendothelial and splenic components of platelet destruction (1,4). Since the spleen normally has the greatest uptake in a ^{111}In -platelet image, these ratios provided an objective measurement to differentiate normal from abnormal uptake.

RESULTS

Patients are grouped according to the mechanism of thrombocytopenia proposed prior to the performance of the ^{111}In -platelet study.

Case reports are summarized in Table 1.

Decreased Production ? Splenic Sequestration (Patients 1 and 2)

Two children with bone marrow production defects—Fanconi's anemia and congenital thrombocytopenia—have been studied as part of a bone marrow transplantation evaluation. Both children had normal recoveries, 82% and 62%, respectively, and slightly shortened survival times of 95 and 136 hr. Organ imaging showed normal splenic uptake, and thus no evidence for splenic sequestration or destruction (Fig. 1). The results of these studies prevented splenectomy from being considered as a therapeutic intervention in these children prior to bone marrow transplantation.

Hemangiomatous Platelet Destruction (Patients 3 and 4)

Two infants with hemangiomas were referred for evaluation. The first infant was 9 mo of age when she presented with thrombocytopenia (platelet count $5 \times 10^9/\text{l}$) and a large perineal and left thigh hemangioma. The parents had noticed swelling and purpura in the area of the hemangioma. Clotting studies revealed disseminated intravascular coagulation with prolonged

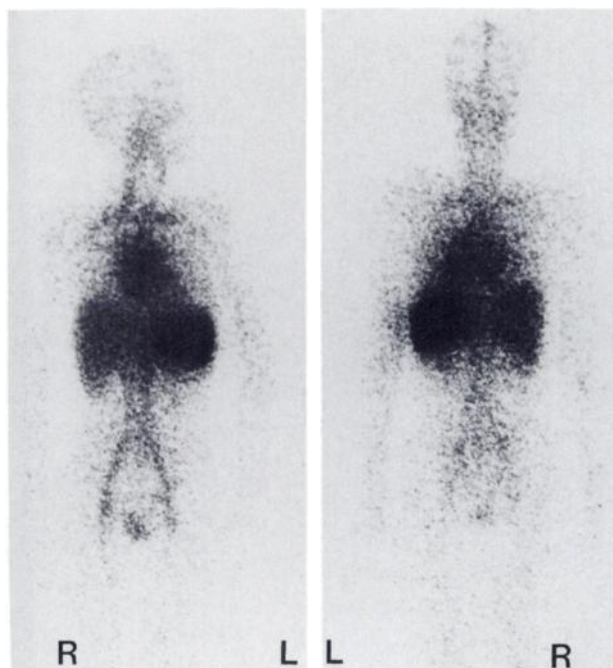


FIGURE 1 Patient 1. Anterior (left) and posterior (right) images obtained 24 hr following injection. In addition to the spleen and liver, activity is noted in the heart, great vessels, and cerebral sinuses, reflecting the normal vascular distribution of platelets in this patient.

screening tests (PT, PTT), low fibrinogen and the presence of fibrin split products. The platelet recovery was 9% and survival time was 20 hr. Organ imaging showed a large hemangioma extending from the thigh to the spleen, and other areas in the axilla and right inguinal regions that were not previously suspected (Fig. 2). Serial images showed increasing activity within the abnormal sites. Along with the very low platelet recovery, this suggested that sequestration of platelets by the hemangiomas contributed to the thrombocytopenia, that was due in large part to destruction of platelets by the hemangioma. This study confirmed that the hemangioma was responsible for the thrombocytopenia and was too extensive for surgical resection. Subsequently, the platelet survival study was used to assess response to several therapeutic interventions including steroids, embolization, and antifibrinolytic therapy. The patient responded well to Amicar (aminocaproic acid), and the platelet count and imaging studies have become normal.

A 17-mo-old female with thrombocytopenia (platelet count $23 \times 10^9/\text{l}$) had a hemangioma of the neck measuring 6 cm \times 4 cm. The recovery was 29% and platelet survival time 2 hr. Surprisingly, organ imaging showed no accumulation in the area of the hemangioma (Fig. 3). As a result, surgical manipulation of the hemangioma was not pursued and further investigation was undertaken. Platelet-associated IgG was elevated

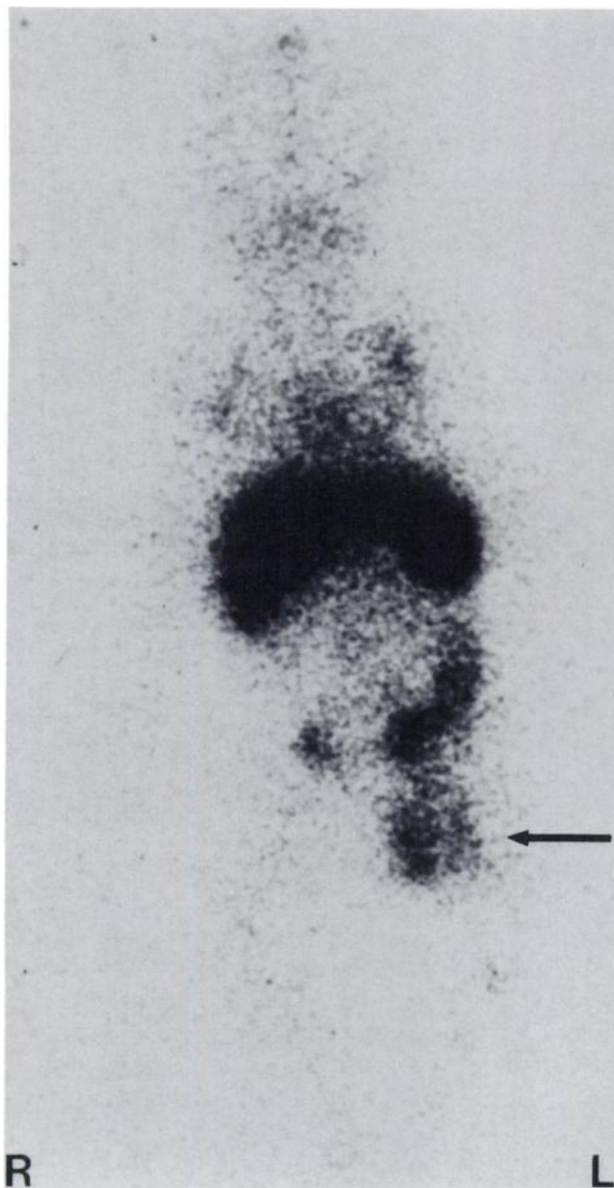


FIGURE 2
Patient 3. Anterior image obtained 24 hr following injection shows multiple areas of abnormal uptake. There is a large area extending from the mid left thigh (arrow) into the abdomen approaching the inferior portion of the spleen. Other foci are noted in the right groin and both axilla. The latter findings were not suspected clinically.

four-fold, bone marrow aspirate revealed increased megakaryocytes, and a diagnosis of immune thrombocytopenia was established. The infant responded to i.v. IgG. In this case, platelet imaging showed the importance of confirming that thrombocytopenia in the presence of a hemangioma is actually due to the hemangioma before pursuing incorrect therapeutic options.

Increased Destruction (Patients 5–10)

Six children with thrombocytopenia of unclear etiology were referred for evaluation. The combined percent

recovery was low (mean 22%) and survival time diminished (mean 16 hr), suggesting increased platelet turnover was responsible for the thrombocytopenia. In Patients 5–8, the site of platelet destruction was the spleen. Furthermore, the scintigraphic findings influenced therapy in several cases. For example, Patient 8 was suspected of having ITP, since elevated platelet associated IgG was present; however, he failed to respond to standard medical therapy including glucocorticoids and i.v. IgG. The ^{111}In -platelet study showed increased splenic uptake (Fig. 4), confirming the role of the spleen in active platelet destruction and suggesting a therapeutic response to splenectomy. Indeed, the platelet count rose to normal following splenectomy.

Patient 9, with ITP, had persistent thrombocytopenia that was refractory to splenectomy. Subsequently, computed tomography revealed the presence of an accessory spleen. To assess its role in the continuing thrombocytopenia, an ^{111}In -platelet study was performed. Surprisingly, the accessory spleen accumulated only 2% of the injected activity (Fig. 5). The remainder accumulated in the liver and lungs, reflecting the activation of other reticuloendothelial components as sites of platelet destruction.

In Patient 10, who had severe aortic insufficiency and thrombocytopenia, an ^{111}In -platelet study was requested to assess the role of the spleen in platelet destruction or sequestration, and the contribution of mechanical destruction of platelets. Antiplatelet antibody tests were negative. Platelet imaging showed increased uptake in both the liver and spleen (Fig. 6), with a much lower than usual spleen:liver ratio (Table 1), suggesting that splenectomy would not cure the thrombocytopenia. The aortic valve was replaced but the thrombocytopenia persisted. However, the platelet count then responded rapidly to glucocorticoids. Splenectomy was once again avoided.

DISCUSSION

Investigation of the mechanism of thrombocytopenia in children was previously difficult because of problems associated with the traditional label ^{51}Cr . The development of [^{111}In]oxine as a platelet label has proven advantageous because of its high labeling efficiency (90%), and medium-energy gamma emissions, which allow high quality organ imaging (1,2,4,6–13). In this report, we describe the use of this technique as part of the investigation of children with thrombocytopenia. The cases presented outline the benefits in clinical investigations that can be derived from the use of this radiolabeling technique in selected patients.

Production defects were shown to be the principal cause of thrombocytopenia in Patients 1 and 2. They were candidates for bone marrow transplantation, which would be accompanied by splenectomy if splenic

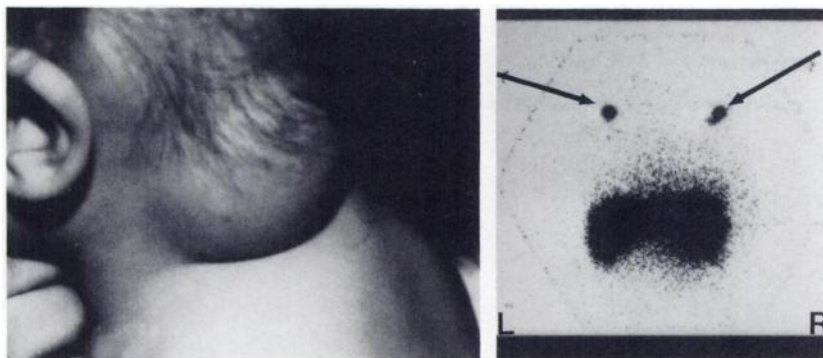


FIGURE 3

Patient 4. A large hemangioma protrudes from the back of the neck. A posterior image, however, shows that the hemangioma does not accumulate platelets. There is however, increased uptake in the spleen and liver. The arrows point to markers on either side of the hemangioma.

sequestration were shown to contribute to the thrombocytopenia. However, the normal platelet recoveries and normal splenic activities effectively ruled out sequestration and splenectomy was avoided.

Patients 3 and 4 had large hemangiomas thought to be responsible for thrombocytopenia. In Patient 3, the ^{111}In -platelet study showed clearly that the hemangioma accumulated platelets. The extent of the hemangioma was much larger than clinically suspected and multiple other sites were demonstrated. Thus, the lesion was not surgically resectable and other forms of therapy were pursued. Though Patient 4 had a large hemangioma of the neck and thrombocytopenia, the ^{111}In -platelet study showed that, unlike the preceding patient, the heman-

gioma was not responsible for the thrombocytopenia. Further investigations showed the patient had immune thrombocytopenia, which resolved after institution of appropriate medical therapy. These cases illustrate the importance of confirming that the hemangioma is indeed responsible for the thrombocytopenia, the value in assessing the extent of the hemangioma when resection is contemplated, and the importance of this technique in following therapeutic interventions.

For patients with increased destruction of platelets, the ^{111}In -platelet studies help document the etiology of the thrombocytopenia, particularly in children who do not fit a readily recognizable presentation for ITP with documented platelet antibody elevations. Furthermore,

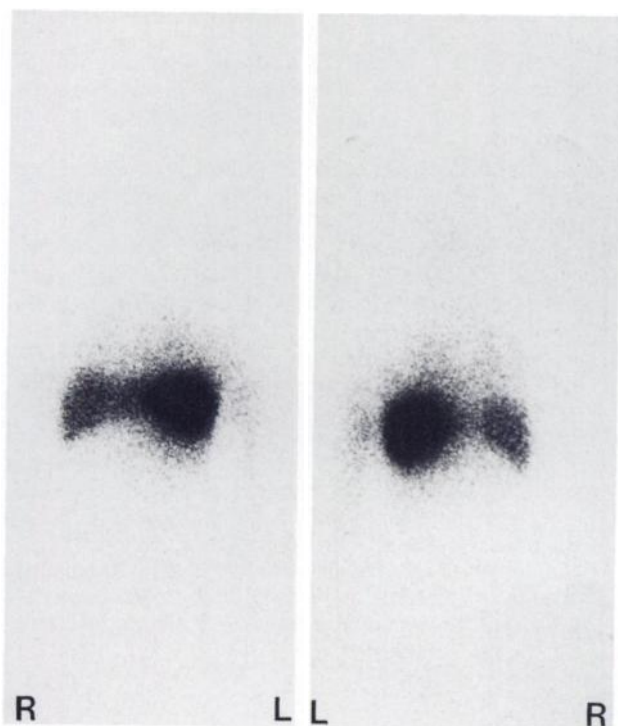


FIGURE 4

Patient 8. Anterior (left) and posterior (right) images obtained 1 hr following injection shows that the spleen appears enlarged and is "hot". Note the absence of cardiac activity reflects the rapid clearance of platelets from the vascular system.

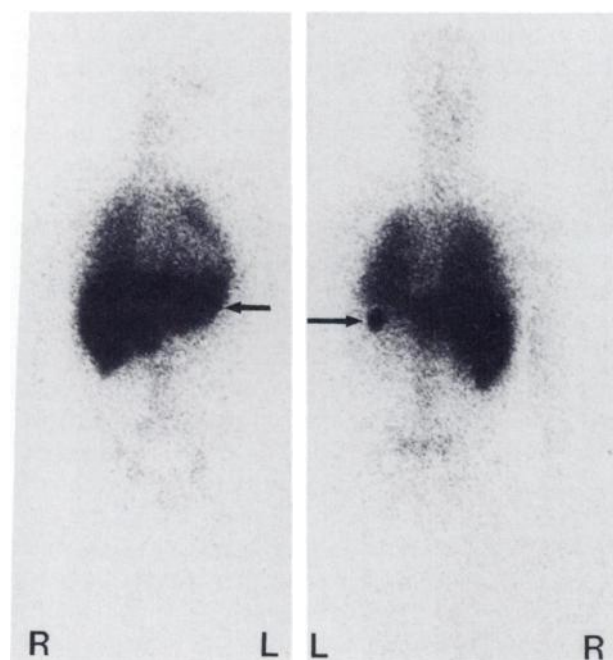


FIGURE 5

Patient 9. Anterior (left) and posterior (right) images show that a small accessory spleen is present (arrow). Most activity appears in the liver and lungs, reflecting activation of the reticuloendothelial system and its role in the clearance of platelets. Faint bone marrow activity is also seen. A photon deficient area in the heart indicates rapid clearance of the platelets from the circulation.

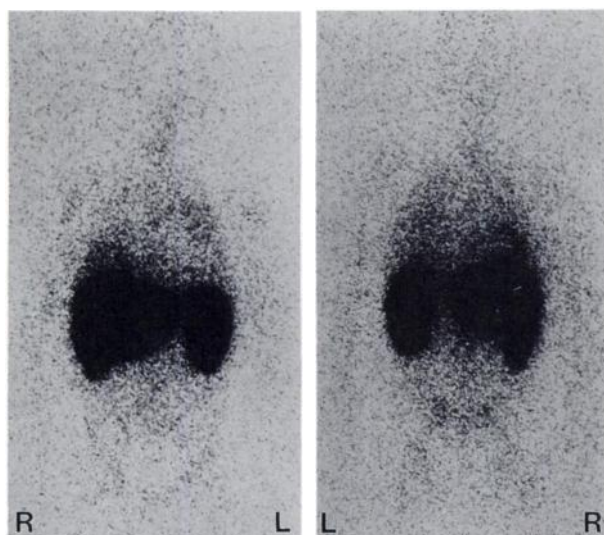


FIGURE 6

Patient 10. The intensity of activity in the spleen appears similar to the liver. Rapid removal of platelets is evident by the lack of activity in the vascular system by 1 hr following injection.

the ^{111}In -platelet study provided clinical information suggesting that the spleen was not solely responsible for the thrombocytopenia, and splenectomy and accessory splenectomy were avoided in two children (Patients 9 and 10). These patients responded to other therapeutic interventions. On the other hand, marked accumulation of platelets was seen in the spleen of Patient 8 and splenectomy resolved the thrombocytopenia. Thus, in patients with thrombocytopenia resulting from increased destruction, these studies can be of great help in directing therapy and avoiding unnecessary splenectomy.

The use of radiolabeled platelet studies in adults is well documented (11–13) but the techniques with [^{111}In]oxine have only recently been adapted for use in children. While this report described only a small number of cases, we have demonstrated the usefulness of this technique in children with thrombocytopenia regardless of suspected etiology, the importance of the study for confirming a clinical diagnosis, and the benefits of the technique for predicting response to a clinical intervention. We believe this study should be performed, when possible, in any child with thrombocytopenia where the mechanism of the thrombocytopenia is unclear or the therapeutic intervention will involve splenectomy or surgical resection of an hemangioma.

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