Transient Reticulocytopenia in Viral Illness

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ABSTRACT

Infection resulting in transient reticulocytopenia and anemia, the so-called "aplastic crisis," has frequently been documented in patients with congenital hemolytic anemia. However, this association with hematologically normal patients has been less well recognized. Its occasional severity is illustrated by this report of two cases of marked reticulocytopenic anemia in association with probable viral infections. These were previously healthy children whose anemias could be explained only by a temporary interruption of erythropoiesis. These patients recovered spontaneously and were in good health one year later. A subsequent separate survey of leukopenic patients with a wide variety of viral infections demonstrated significant reticulocytopenia in seven of 35 patients (20 percent). It is concluded that in addition to the more widely appreciated neutropenia and thrombocytopenia of viral infections, reticulocytopenia is a common manifestation of many viral infections and may occasionally result in profound anemia.

Introduction

The leukopenic and less frequent thrombocytopenic effects of viral infections upon hematopoiesis are well known. Reticulocytopenia is also said to be common in viral infections; however, that association seems less well appreciated, probably because reticulocyte counts are not ordinarily performed in the diagnosis and management of most viral infections. Anemia owing to depressed erythropoiesis with reticulocytopenia has been frequently described in association with a variety of congenital hemolytic states, particularly hereditary spherocytosis and sickle cell anemia. Although these "aplastic crises" with erythropoietic arrest are frequently thought to be idio­pathic in nature, many have been ascribed to infections, particularly viral infections. Obviously, in those hemolytic diseases...
associated with poor red cell survival, a transient hiatus in erythropoiesis may quickly result in significant anemia. On the other hand, since normal erythrocytes enjoy a survival approximating 120 days, erythropoietic arrest to cause clinically significant anemia must be present for a period of at least several weeks. Transient erythroblastopenia of childhood, that is, temporary anemia, reticulocytopenia, and narrow erythroblastopenia, have been described far less frequently in otherwise hematologically normal patients.\textsuperscript{1}

Having recently encountered two dramatic cases of severe anemia with transient reticulocytopenia in normal children, it was suggested that viral suppression of erythropoiesis may be far more common than is generally appreciated. To evaluate further possible transient depression of erythropoiesis, reticulocyte counts have been performed in a variety of clinically diagnosed viral illnesses as they were presented to our institution. It is the purpose of this report to emphasize the frequency of transient reticulocytopenia by describing two new cases of transient erythroblastopenia, as well as to report the results of the survey of reticulocytes in a group of patients with a variety of viral illnesses.

**Patients and Methods**

The two case reports consisted of routine pediatric admissions for the study and treatment of anemia in 1978 and 1979 at St. Joseph’s Hospital, Tampa, Florida.

A second group of patients was studied to determine if reticulocytopenia could be detected in a variety of viral illnesses. Both inpatients and outpatients were studied on the basis of a presenting complete blood count (CBC) report. Selected for study were those patients whose CBC’s suggested a viral illness, that is, exhibited primarily an absolute neutropenia, (2,500 per cmm), with a relative or absolute lymphocytosis and with or without reactive forms. Patients with cancer or those receiving radiation or chemotherapy, which are known to be associated with marrow depression, were excluded from the study. Once a patient was selected for inclusion in the study, a reticulocyte count was performed within 24 hours on the portion of blood left over from the CBC. The reticulocyte preparations were stained with new methylene blue, and the percentage of reticulocytes was based upon a count of 1,000 red blood cells and converted to absolute numbers of reticulocytes utilizing the total red blood cell count as determined by the Coulter S Plus.

Total reticulocyte counts of less than 0.5 percent of erythrocytes or 21,000 per cmm for females and 23,000 per cmm for males were considered to be reticulocytopenic.\textsuperscript{20} All low reticulocyte counts were verified by one of the authors. A total of 52 cases was included in this study. A diagnosis of “viral disease” was based upon the history and physical findings augmented by the usual laboratory studies available in a clinical setting. Some patients were inpatients, while others were seen in the Emergency Room. Laboratory studies included many bacterial cultures and some viral serological tests, but most diagnoses of “viral disease” were of a clinical nature and did not include specific serological confirmation or agent isolation.

**Case Reports**

**CASE 1.** The patient was a 17 month old white female who, when seen for a sore throat and fever, was found to be anemic. Hemoglobin and hematocrit results at that time were 6.8 g per dl and 20 percent, respectively. The reticulocyte count was 0 percent. The patient’s past medical history was essentially unremarkable, except for a presumably viral upper respiratory tract infection, three months previously, and gastroenteritis with diarrhea, two months previously. Recovery from each was prompt and complete. The family history included no evidence of anemia, excepting for the maternal grandmother who had iron deficiency anemia at one time.

Upon admission, the patient’s temperature was 101°F and pulse rate was 120 per min. She was well developed and nourished with a height and weight
TABLE I
Hematological Parameters of Case 1

<table>
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<tr>
<th>Date</th>
<th>RBC's million/cmm</th>
<th>Hemoglobin gm/dl</th>
<th>Hematocrit percent</th>
<th>WBC's /cmm Total Granulocytes /cmm</th>
<th>Total Lymphocytes /cmm</th>
<th>Platelets thousand /cmm</th>
<th>Reticulocytes (percent of RBC's)</th>
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<tr>
<td>4/18/79</td>
<td>6.8</td>
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<td></td>
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<td>4.8</td>
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<td>4/24/79</td>
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<td>9/20/79</td>
<td>11.2</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.2</td>
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<td>1/8/80</td>
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<td>37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.2</td>
</tr>
</tbody>
</table>

...in the 50th percentile. Physical examination was normal except for pallor and a grade I systolic murmur along the left sternal border.

The CBC on admission showed: hemoglobin, 6.9 g per dl; hematocrit, 17.2 percent; white blood count, 7,200 per cmm with 2 percent segmented neutrophils and 98 percent normal lymphocytes. The platelet count was 260,000 per cmm and a repeat reticulocyte count was 0 percent. The urinalysis was normal. A chest x-ray showed no abnormality. Throat and nasopharyngeal cultures demonstrated only the usual bacterial flora. Further hematologic tests included: serum iron, 163 µg per dl; iron binding capacity, 250 µg per dl; normal hemoglobin electrophoresis with A1 = 97.1 percent, A2 = 2.6 percent; and total hemoglobin, 0.3 percent. Stools were negative for occult blood, and both the direct and indirect Coomb's tests were negative.

An iliac crest bone marrow done on the day of admission had an estimated cellularity of 50 percent and a myeloid:erythroid (M:E) ratio of 10:1. Normoblastic erythroid precursors were present. While pronormoblasts and basophilic normoblasts were conspicuous and possibly slightly increased, the polychromatophilic and orthochromic forms were markedly decreased. Granulocytic and megakaryocytic elements were unremarkable. Stable hemosiderin was slightly increased.

The patient's anemia was monitored by serial reticulocyte and blood counts. No transfusions, antibiotics, or steroids were given. Over the six day hospital stay, the reticulocyte counts gradually rose from 0 to 9 percent. A concomitant rise in hemoglobin and hematocrit was noted (table I). Follow-up studies by the pediatrician revealed a hemoglobin of 11.2 g per dl, hematocrit, 37 percent, and reticulocytes, 2.8 percent five months following discharge. At nine months following hospitalization, these values were 11.8 g per dl, 37 percent and 2.2 percent, respectively.

CASE 2. A white male who was first noted to be pale 10 days prior to being seen by a pediatrician. Examination confirmed anemia:

TABLE II
Hematological Parameters of Case 2

<table>
<thead>
<tr>
<th>Date</th>
<th>RBC's million/cmm</th>
<th>Hemoglobin gm/dl</th>
<th>Hematocrit percent</th>
<th>WBC's /cmm Total Granulocytes /cmm</th>
<th>Total Lymphocytes /cmm</th>
<th>Platelets thousand /cmm</th>
<th>Reticulocytes (percent of RBC's)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/30/79</td>
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</table>
hemoglobin, 5.6 g per dl, hematocrit, 16.2 percent, and reticulocytes, 0 percent. The child's appetite and food intake had been normal, and there was no history of melena. The child had been seen on a routine check-up two months earlier at which time his hemoglobin was 13.5 g per dl.

The child had previously been in good health except for a skin rash one month earlier which responded to small doses of diphenhydramine hydrochloride. Two upper respiratory tract infections occurred prior to that, and these were regarded as of viral etiology, having responded quickly to symptomatic therapy. No other drugs had been taken, and there was no exposure to toxins. There was no family history of anemia.

Upon admission, the patient's temperature was 100.2°F and pulse rate was 120 per min. Except for pallor, this well nourished, active child's physical examination was normal. Laboratory examinations included: urinalysis = normal; direct Coomb's test = negative; stools for occult blood = negative; osmotic fragility = normal; serum iron, 157µg per dl; iron binding capacity, 332µg per dl; haptoglobin, 81 mg per dl (normal, 60 to 270); and red cell glucose-6-phosphate dehydrogenase, 5.7IU per g Hb (normal, 5 to 9). Cultures of urine, blood, throat, and stool were either negative or contained normal flora. A chest x-ray was normal. A bone marrow from the iliac crest on the second hospital day, when the reticulocyte count was 0.2 percent, was 60 percent cellular with a myeloid:erythroid (M:E) ratio of 3:1. Normal erythroid elements of all stages of maturation were present, although pronormoblasts and basophilic normoblasts appeared increased. Stainable hemosiderin was slightly increased. Lacking evidence of hemolysis, these findings were interpreted as a signal of marrow recovery, suggesting that reticulocytosis would soon follow.

The patient was observed in the hospital for eight days with the first evidence of reticulocytosis occurring on the fourth hospital day. The only treatment consisted of 100 ml of packed red cells on the fourth day. His hematological parameters are portrayed in Table II. On the day of discharge, the patient's hemoglobin was 9.8 g per dl and hematocrit was 29.6 percent. One month later, the hemoglobin was 12 g per dl, hematocrit, 36 percent, and reticulocytes, 1.8 percent, while at the one year follow-up, the hemoglobin was 14 g per dl and the hematocrit, 40 percent.

Results of Survey of Reticulocyte Counts in Viral Diseases

Of the 52 patients with neutropenia, review of clinical and laboratory data allowed a diagnosis of uncomplicated and untreated viral disease in 35 of them. The remaining 17 neutropenic patients were excluded, since they were frequently receiving drug therapy which might have been myelosuppressive. Additionally, their inflammatory processes appeared non-viral and usually bacterial in nature (nine cases), or there was no evidence of an acute inflammatory process (eight cases).

Seven of the 35 cases (20 percent) of viral disease had reticulocytopenia as defined. Two of these reticulocytopenic patients were also mildly thrombocytopenic, and five of them were under 16 years of age. The various hematological parameters and clinical diagnoses of these seven patients are portrayed in Table III.

Discussion

Failure of the bone marrow to produce erythrocytes, granulocytes, and thrombocytes with resulting pancytopenia is designated “aplastic anemia.” Various degrees of this condition are encountered in clinical practice, extending from the classical aplastic anemia with severe generalized marrow hypocellularity and marked peripheral pancytopenia to less profound hypoplastic conditions associated with cytopenias of lesser degree.

Marrow suppression has been ascribed to a wide variety of etiologies, ranging from foreign substances (chemicals, toxins, and drugs) to infectious agents (primarily bacterial and viral) to associated neoplasia (thymoma, preleukemic states). The largest single category, however, remains the idiopathic cases.

It is quite probable that viral infections will be increasingly incriminated in many of the cases that are now regarded as idiopathic. Viral hepatitis is one form of viral illness which has been implicated not only in complete marrow aplasia, but also in transient red cell aplasia. Prior to 1955, this form of infection was not considered to be of etiologic importance in aplastic anemia. However, since that time numerous case reports involving type A, type B, and non A and non B viral hepatitis have been documented. Although Coomb's negative hemolytic forms of anemia have been associated with viral hepatitis, the anemia is
### TABLE III

Hematological Parameters and Clinical Diagnoses of Seven Reticulocytopenic Patients with Viral Disorders

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>RBC* million /cmm</th>
<th>Hgb† gm/dl</th>
<th>Hct‡ Per- cent</th>
<th>Platelets thousand /cmm</th>
<th>N.† WBC /cmm</th>
<th>N.G.§ Lymphocytes /cmm</th>
<th>Days</th>
<th>Since</th>
<th>Onset</th>
<th>Clinical Diagnoses</th>
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</thead>
<tbody>
<tr>
<td>CK</td>
<td>F</td>
<td>30</td>
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<td>12.7</td>
<td>37.7</td>
<td>142</td>
<td>12,399</td>
<td>2,700</td>
<td>459</td>
<td>1</td>
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<td>128</td>
<td>3,620</td>
<td>910</td>
<td>5,810</td>
<td>10</td>
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<td>DL</td>
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<td>4.56</td>
<td>13.0</td>
<td>38.9</td>
<td>241</td>
<td>13,680</td>
<td>3,700</td>
<td>459</td>
<td>1</td>
<td></td>
<td>Chicken pox</td>
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<td>TM</td>
<td>M</td>
<td>9</td>
<td>4.74</td>
<td>13.4</td>
<td>40.3</td>
<td>177</td>
<td>9,480</td>
<td>897</td>
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<td></td>
<td>Acute gastro- enteritis</td>
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<tr>
<td>DM</td>
<td>M</td>
<td>16</td>
<td>5.03</td>
<td>15.3</td>
<td>46.3</td>
<td>134</td>
<td>20,120</td>
<td>2,133</td>
<td>459</td>
<td>2</td>
<td></td>
<td>Rubella</td>
</tr>
<tr>
<td>KB</td>
<td>M</td>
<td>24</td>
<td>4.36</td>
<td>10.9</td>
<td>32.5</td>
<td>295</td>
<td>21,800</td>
<td>644</td>
<td>3,450</td>
<td>3</td>
<td></td>
<td>Viral exanthem</td>
</tr>
</tbody>
</table>

*Hemoglobin  
†Hematocrit  
‡Reticulocytes  
§Neutrophilic granulocytes  
%Lymphocytes

accounted for more commonly on the basis of marrow suppression as reflected by low reticulocyte counts. Complete marrow failure as found in viral hepatitis is associated with a predominantly adult male population during the recovery phase of the hepatitis.\(^3\)\(^5\)\(^8\)\(^9\) It is unrelated to the severity of the hepatitis and has a survival rate of only 12 to 15 percent.\(^15\)

A similar although less frequent association of bone marrow suppression has been noted in infectious mononucleosis. Although hemolytic anemia is more frequently observed, aplastic anemia has manifested itself via granulocytopenia, thrombocytopenia, and, least commonly, pancytopenia.\(^10\)\(^13\)\(^19\) Van Doornik et al believe that infection with Epstein Barr virus should be added to the list of possible causes of aplastic anemia.\(^19\)

The unique suppression of the erythroid cell line in association with infectious diseases, particularly viral illnesses, has been observed for many years in the so-called "aplastic crises" of a variety of congenital hemolytic anemias. Obviously, in these types of anemia, a small hiatus in red cell production can quickly result in significant anemia. The most common forms of hemolytic anemia that have been associated with such crises are congenital spherocytic anemia and sickle cell disease, although similar crises have been documented in many other forms of hemolytic anemia as well.\(^6\)\(^7\)\(^12\)

Further data linking viral illness and erythroid cell line suppression has been compiled by Alter and Nathan.\(^1\) Approximately 60 cases have been reported of transient erythroblastopenia in children, all of whom have suffered some form of viral illness two weeks to two months prior to the development of pallor. All of these patients were between the ages of one month and six years and all presented with anemia and reticulocytopenia. Subsequent bone marrow examinations showed erythroid hypoplasia. Prognosis, however, was excellent with patients recovering usually within one to two months and often with no treatment.

The two cases which are the subject of this report serve to illustrate further the association between viral illness and the depression of erythropoiesis with resultant anemia. While only one of our cases appears to be pure red cell hypoplasia, the other exhibiting granulocytopenia as well, there is no question that the principal clinical manifestations were related to anemia. Furthermore, since these two cases appeared at our hospital within a relatively short period of time, the authors suggested that virus-induced suppression of erythropoiesis as particularly manifested by reticulocytopenia might be
more common than is generally appreciated. That this is a fact is substantiated by our study of 35 cases in which seven or 20 percent of the patients were found to have reticulocytopenia.

The specific mechanisms by which the marrow and, in particular the erythroid cell line, is depressed in viral illnesses are unclear. While it is probable that a variety of viruses may cause marrow depression, it is uncertain whether or not their manner of action is similar in all cases. Certain clinical presentations, such as those in our series of the seven reticulocytopenic patients, suggest a sudden and direct action against the marrow. Whether or not this could represent a direct cellular or chromosomal insult wrought by a virus, or a toxin resulting from a virus-induced metabolic pathway interruption, is only speculative. Other clinical settings, i.e., those described in our two case reports, suggest a more indirect, time-consuming process such as the slow buildup of an immunologic surge or the gradual replication of an altered virus exhibiting a hematodepressive potential.9-11

In any event, despite the lack of unanimity regarding mechanisms, it appears that viral depression of bone marrow hematopoietic elements is a well substantiated phenomenon. Moreover, particular depression of the erythroid precursors may occur, sometimes resulting only in a peripheral reticulocytopenia but occasionally yielding marrow erythroblastopenia and anemia. Finally, it is possible that common and frequently trivial or subclinical viral infections may be responsible for many cases of marrow depression that are currently regarded as idiopathic in nature.

References