BRIEF NOTE

Erythroid Hypoplasia Associated with Chloramphenicol Therapy

By FARUK L. OZER, WAYNE E. TRUAX AND WILLIAM C. LEVIN

THE EFFECTS of large doses of chloramphenicol on the human hematopoietic system have been reported only once previously.15 A patient recently seen by us inadvertently received 12 Gm. of chloramphenicol daily for 14 days. Serious hematologic manifestations appeared during the course of treatment. The present report describes this phenomenon.

CASE REPORT

J. F., No. 42008-M. The patient, a 20 year old white female, was admitted to the hospital on July 10, 1957, "for the enlargement of the neck and eyes." Diagnosis of Graves' disease was made and a therapeutic dose of 12.3 mc. of I131 was administered.

On November 5, 1957, she was readmitted on the ophthalmology service because of the development of malignant exophthalmos with corneal ulceration of the left eye. She was still mildly hypothyroid. Her weight was 114 pounds. A blood count on admission revealed the following: Hemoglobin 11.9 Gm. per cent, WBC 6300 cu.m., with PMN 81 per cent, stab forms 2 per cent, lymphocytes 16 per cent, monocytes 1 per cent. She was treated with Diamox 250 mg. 4 times a day and a sulfonamide preparation, Gantrisin 2 Gm. every six hours, orally. Administration of prednisone, 10 mg. every six hours, and aqueous penicillin, 1,000,000 units every four hours, was begun two days later. Through some misunderstanding, the patient also received chloramphenicol 3 Gm. every six hours for 14 days. One week later the dose of prednisone was increased to 20 mg. every six hours. The administration of triiodothyronine 50 mc. every six hours and ACTH gel 40 units every 12 hours was begun.

On November 13, 1957, she was seen in consultation because of nausea with vomiting of small amounts of blood. Physical findings were unchanged except that the tongue had become beefy red. A blood count revealed: hemoglobin 12.1 Gm. per cent, WBC 10,300 cu.mm., with PMN 93 per cent, lymphocytes 5 per cent, and monocytes 2 per cent. A platelet count was not done at that time. Bleeding time was 1 minute and 15 seconds, clotting time 3 minutes and 20 seconds. X-ray examination of the upper gastrointestinal tract was negative. The next day bleeding from the gums and nose began and large hematomas developed at the sites of injections.

Review of the nurses' notes revealed the previously unnoticed large dose of chloramphenicol. On November 18, 1957, the one-stage prothrombin time was 10 per cent of normal. The next day the hemoglobin value was 9.4 Gm. per cent, and the platelet count was 75,000 cu.mm.* Serial blood counts are shown in table 1. Results of liver function studies were within normal limits except for a 4+ cephalin flocculation after 48 hours. A direct Coombs' test was negative.

The patient was given 50 mg. of vitamin K1 oxide intravenously with almost immediate cessation of all bleeding. A bone marrow aspiration performed on November 20, 1957,

From the Department of Internal Medicine and Hematology Research Laboratory, University of Texas Medical Branch, Galveston, Tex.

Submitted July 21, 1959; accepted for publication Dec. 10, 1959.

*Daneshk's indirect method.
Table 1.—Serial Peripheral Blood Counts Before, During and Following Recovery from Erythroid Hypoplasia

<table>
<thead>
<tr>
<th>DATE</th>
<th>RBC .10^6</th>
<th>Hb .Gm%</th>
<th>RETICULOCYTES .%</th>
<th>WBC</th>
<th>PAN</th>
<th>STAB FORMS</th>
<th>MYELOBLASTS</th>
<th>ERYTHROBLASTS</th>
<th>MACROCYTES</th>
<th>MONOCYTES</th>
<th>PLATELETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/5/57</td>
<td>--</td>
<td>11.9</td>
<td>--</td>
<td>6,300</td>
<td>81</td>
<td>2</td>
<td>--</td>
<td>--</td>
<td>1</td>
<td>16</td>
<td>--</td>
</tr>
<tr>
<td>11/14/57</td>
<td>--</td>
<td>12.1</td>
<td>--</td>
<td>10,300</td>
<td>93</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2</td>
<td>5</td>
<td>--</td>
</tr>
<tr>
<td>11/18/57</td>
<td>3.4</td>
<td>9.8</td>
<td>--</td>
<td>5,700</td>
<td>91</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1</td>
<td>8</td>
<td>--</td>
</tr>
<tr>
<td>11/19/57</td>
<td>3.75</td>
<td>9.4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>11/20/57</td>
<td>3.69</td>
<td>7.1</td>
<td>0.4</td>
<td>11,800</td>
<td>49</td>
<td>5</td>
<td>1</td>
<td>--</td>
<td>18</td>
<td>27</td>
<td>81,180</td>
</tr>
<tr>
<td>11/22/57</td>
<td>3.50</td>
<td>7.1</td>
<td>0.2</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>250,200</td>
</tr>
<tr>
<td>11/25/57</td>
<td>3.48</td>
<td>8.3</td>
<td>8.4</td>
<td>13,100</td>
<td>88</td>
<td>1</td>
<td>5</td>
<td>--</td>
<td>5</td>
<td>3</td>
<td>229,680</td>
</tr>
<tr>
<td>11/27/57</td>
<td>4.01</td>
<td>9.0</td>
<td>16.8</td>
<td>10,150</td>
<td>92</td>
<td>--</td>
<td>1</td>
<td>--</td>
<td>4</td>
<td>3</td>
<td>561,000</td>
</tr>
<tr>
<td>11/29/57</td>
<td>4.32</td>
<td>10.1</td>
<td>8.5</td>
<td>17,050</td>
<td>91</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>5</td>
<td>4</td>
<td>545,000</td>
</tr>
<tr>
<td>12/2/57</td>
<td>4.63</td>
<td>10.3</td>
<td>15.6</td>
<td>17,000</td>
<td>93</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3</td>
<td>4</td>
<td>885,120</td>
</tr>
<tr>
<td>12/6/57</td>
<td>4.87</td>
<td>10.7</td>
<td>4.4</td>
<td>9,100</td>
<td>75</td>
<td>1</td>
<td>1</td>
<td>--</td>
<td>4</td>
<td>10</td>
<td>430,000</td>
</tr>
<tr>
<td>12/9/57</td>
<td>5.17</td>
<td>10.4</td>
<td>5.2</td>
<td>12,800</td>
<td>82</td>
<td>1</td>
<td>1</td>
<td>--</td>
<td>9</td>
<td>7</td>
<td>351,560</td>
</tr>
<tr>
<td>12/13/57</td>
<td>4.38</td>
<td>11.3</td>
<td>3.2</td>
<td>12,300</td>
<td>76</td>
<td>--</td>
<td>3</td>
<td>--</td>
<td>3</td>
<td>12</td>
<td>714,680</td>
</tr>
<tr>
<td>2/28/58</td>
<td>4.72</td>
<td>10.9</td>
<td>2.4</td>
<td>5,050</td>
<td>75</td>
<td>2</td>
<td>1</td>
<td>--</td>
<td>9</td>
<td>13</td>
<td>530,000</td>
</tr>
</tbody>
</table>

*BEFORE THE BEGINNING OF THERAPY
†CHLORAMPHENICOL DISCONTINUED

revealed normal cellularity (fig. 1). The myeloid elements showed extreme "toxic" granulation. The most impressive finding was the pronounced hypoplasia of the erythroid series. Megaloblasts were the only nucleated erythroid elements seen. Megakaryocytes were also scanty. At this point chloramphenicol, Diamox and Gantrisin were discontinued. As shown in table 1, hemoglobin and erythrocyte levels remained depressed until November 25, 1957, at which time a reticulocytosis appeared. The next day bone marrow examination revealed numerous normoblasts; thereafter, progressive hematologic improvement ensued. On December 4, 1957, the bone marrow was found to be hypercellular with a marked normoblastic reaction. One week later erythroid hyperplasia was still present. "Toxic" granulation of the myeloid elements were less marked and megakaryocytes appeared normal. The "glossitis" had also disappeared. The patient was challenged with Diamox, 250 mg. every 12 hours on November 29, 1957, and with 500 mg. of Gantrisin on December 5, 1957, without untoward effects. Right orbital decompression was performed on December 20, 1957, and bilateral tarsorrhaphy on February 5, 1958. The patient was discharged on March 5, 1958, with only a corneal scar on the left eye. When the patient was last seen on October 13, 1958, the blood picture was normal and she was euthyroid.

**COMMENT**

Because of malignant exophthalmos with an infected cornea, this patient received a multitude of drugs. Of these, sulfisoxazole (Gantrisin), acetazol-

*The Sabin-Doan terminology is used for nucleated red blood cells in this report.
ERYTHROID HYPOPLASIA AFTER CHLORAMPHENICOL

Fig. 1.—Marrow film showing erythroid hypoplasia during the period of chloramphenicol administration. One megaloblast is the only erythroid form seen.

Fig. 2.—Marrow film showing hypercellularity with pronounced erythroid stimulation, taken five days after marrow in figure 1 and five days after chloramphenicol administration was discontinued.
amide (Diamox), two sulfonamides\(^1\) and chloramphenicol were the possible offending agents to account for production of transient erythroid hypoplasia with maturation arrest and thrombocytopenia, since other medications were continued during the course of the hematologic complication without affecting the subsequent course.

Hematologic side effects of sulfonamides appear mainly as granulocytopenia,\(^1\) hemolytic anemia\(^2\) and very rarely as aplastic anemia\(^1\) and thrombocytopenia.\(^3\) Granulocytopenia may be related to either hypersensitivity or direct toxic effects of sulfonamides. In the case of hemolytic anemia, in addition, there may be some inherited metabolic abnormalities of the red cells.\(^5\) Aplastic anemia and thrombocytopenia appear to be related to individual hypersensitivity, particularly because of their rare occurrence with sulfonamides, and since the doses need not necessarily be large. A hypersensitivity phenomenon in the patient under discussion seems unlikely, since challenging doses of both sulfisoxazole and acetazolamide did not produce any changes in the bone marrow and peripheral blood. Therefore, chloramphenicol appears to be the responsible agent. Chloramphenicol therapy has been reported to coincide with agranulocytosis,\(^7\) thrombocytopenia,\(^8\) aplastic anemia,\(^9\) hemolytic anemia\(^10\) and bone marrow depression.\(^11\) These side effects of chloramphenicol are generally accepted. In the above instances daily doses of chloramphenicol have usually been within usually recommended therapeutic limits.

Large doses (8 to 12 Gm. daily) of this drug were given to patients with advanced carcinoma by Krakoff et al.\(^12\) Every patient developed anemia with reticulocytopenia, and a few also had leukopenia and thrombocytopenia. Bone marrow examinations, however, revealed normal cellularity with some minor abnormalities in the myeloid elements. Other side effects included nausea, vomiting and "glossitis." With cessation of therapy, peripheral blood changes reverted to normal and "glossitis" disappeared. Although small repeated doses were ineffective, the same effects were reproduced with large doses.

Our case is comparable to those reported by Krakoff et al. In addition to anemia and reticulocytopenia, there also occurred severe erythroid hypoplasia with maturation arrest, decrease of megakaryocytes in the bone marrow and severe bleeding tendency. Leukocytes showed only so-called toxic granulations. Although a hypersensitivity phenomenon cannot definitely be excluded in the present case, the similarities between this and the cases of Krakoff and associates lead us to believe that the marrow hypoplasia was due to direct toxic effect of chloramphenicol. Erythropoietic depression attributable to chloramphenicol, utilizing ferrokinetic methods, has been reported.\(^13\) It is interesting that our patient was receiving full steroid therapy during the entire course of the disease; this did not appear to offer any protection against the development of the hematologic complication. It is also apparent that the steroids did not hasten recovery from the hypoplastic state. The ineffectiveness of corticosteroids in the treatment of this complication has been previously reported.\(^15\) The bleeding tendency exhibited by our patient may be explained
on the basis of thrombocytopenia and severe hypoprothrombinemia. The latter may have resulted from sterilization of the intestine with production of a vitamin K deficiency.

**SUMMARY**

1. A case of transient erythroid hypoplasia with maturation arrest and thrombocytopenia probably due to a large dose of chloramphenicol is reported.
2. The literature is briefly surveyed.

**SUMMARIO IN INTERLINGUA**

1. Es reportate un caso de transiente hypoplasia erythroide con arresto de maturation e con thrombocytopenia, dehite probablemente a un grande dose de chloramphenicol.
2. Un breve revista del litteratura es presentate.

**REFERENCES**

Brief Note: Erythroid Hypoplasia Associated with Chloramphenicol Therapy

FARUK L. OZER, WAYNE E. TRUAX and WILLIAM C. LEVIN

Updated information and services can be found at:
http://www.bloodjournal.org/content/16/1/997.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml