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ERYTHROBLASTOPENIA AND LEUKOPENIA IN THE PATIENT WITH SEVERE HERPES ZOSTER TREATED WITH INTRAVENOUS ACYCLOVIR*

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Herpes zoster is an acute infection characterized by crops of vesicules, usually confined to a dermatome, and by pain in the same area. Postherpetic secondary bacterial infections may occur. Antiviral agents such as vidarabine (adenine arabinoside) have been used to treat patients with severe or disseminated zoster. Acyclovir (Zovirax, a product of Wellcome Foundation, Ltd) is well-known as having in vitro activity against the Herpes group of viruses[1-2]. In addition, acyclovir has been shown to be effective in herpes zoster[3, 4].

We present a patient with severe herpes zoster in whom transient erythroblastopenia and leukopenia were observed on the second day of therapy with acyclovir. As far as we know, this is the first such case to be reported in the literature.

Case Report

A seven-year-old girl was admitted to Dr. Sami Ulus Children's Hospital with complaints of severe thigh pain and eruptions. There was no history of varicella.

Physical examination revealed dense, erythematous macular and vesicular eruptions on the left thigh, lower left back and left labium majora, which became sparse at the midline level (Fig. 1). Other findings were normal.

Laboratory studies revealed a throat culture yielding group A beta hemolytic streptococci. Urinalysis was normal. Hemoglobin was 12.4 g/dl, red blood cells 4.34 million per mm^3, hematocrit 34.6 %, white blood cell count 6800 per mm^3 with 38 % neutrophils, 60 % lymphocytes, and 2 % band forms. The erythrocyte sedimentation rate was 6 mm per hour. The varicella-zoster virus was demonstrated by cytopathic effects on the cell culture in the Department of Virology, Hifzisihha Institute, Ankara.

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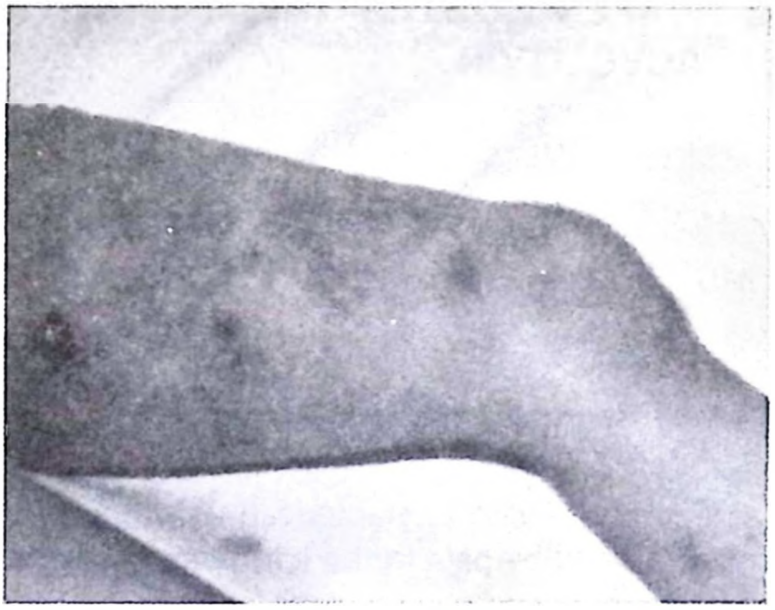

Fig. 1: Hemorrhagic and necrotic vesicles on the left thigh.

Intravenous acyclovir infusion in doses of 5 mg/kg every eight hours was begun. Each vial of Zovirax used for I.V. infusion was reconstituted by the addition of 10 ml physiologic saline. This provided a solution that contained 25 mg acyclovir per ml. 120 mg of acyclovir (5 mg x 24 kg of body weight) were added to 100 ml 0.9 % NaCl, which was given within an hour.

On the second day of therapy no new eruptions were seen. The vesicles were demarcated, and some began to form crusts. Hemoglobin was 10.5 g/dl, hematocrit 31 %, red blood cells 4.3 million per mm^3, and white blood cell count 5000 per mm^3. On the third day, the hemoglobin fell to 9.9 g/dl, red blood cells were 3.2 million per mm^3, and white blood cell count 4000 per mm^3. The erythrocytes were normochromic and normocytic. Bone marrow aspiration showed a decrease in the number of erythroblasts and a relative increase in the number of promyelocytes and myelocytes (Fig. 2). Phenoxymethyl penicilin

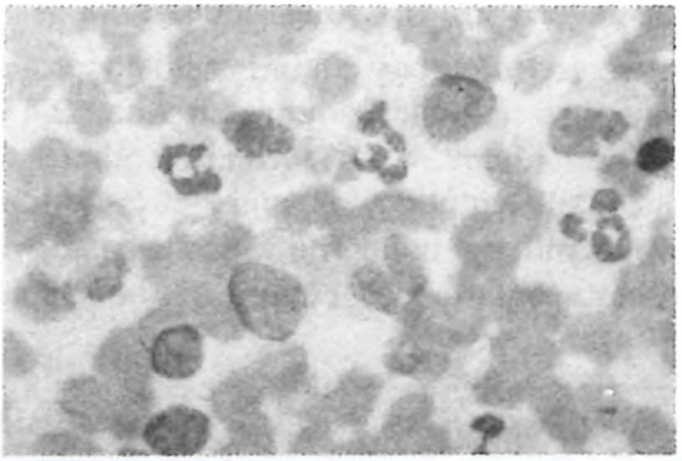

Fig. 2: On the third day, myelocytes and promyelocytes increased and erythroid precursors decreased in the bone marrow aspiration.

(penicillin V) 50,000 U/kg p.o. was started because of a positive throat culture. At the end of the third day of therapy the body temperature dropped to normal and all the vesicles had formed crusts. On the fifth day of therapy hemoglobin was 9.9 g/dl, red blood cells 4 million per mm^3, and white blood cell count 2800 per mm^3. Therapy was discontinued at the end of the fifth day. On the seventh day, hemoglobin, red blood cells, and white blood cells were normal. During the course of therapy, platelets, serum creatinine, creatinine clearance and serum transaminases were normal; direct Coombs test, and cold and warm agglutinins were negative. Normal bone marrow morphology was seen in the control aspiration in the second week. The clinical and hematological courses of the patient are shown in Table 1.

TABLE I. Summary of the Hematological Findings of the Patient

DAYS	1	2	3	4	5	6	7
Hemoglobin (g/dl)	12.4	10.5	9.9	9.9	9.9	11	12
Red blood cells (million/mm^3)	4.34	4.3	3.2	3.5	4	4.5	4.3
Hematocrit (%)	34	31	26	26	29	32	34
White blood cell count (per mm^3)	6800	5000	4000	3800	2800	3600	5800

Discussion

Acyclovir is converted to its monophosphate by the herpes virus enzyme, thymidine kinase. Host cell enzymes add a second and third phosphate group to form acyclovir diphosphate and acyclovir triphosphate. Acyclovir triphosphate is both a competitive inhibitor and a substrate for viral DNA polymerase, but shows little interaction with normal cell DNA polymerase[5].

Instances of transient rises in blood urea and creatinine have been reported after the administration of intravenous acyclovir[6]. The changes have been reversible on cessation of therapy and have sometimes resolved even while therapy was continued. A transient rise in serum transaminases has also been seen. A limited number of local reactions at the injection site has been reported[7].

Evidence of hematopoietic suppression has not yet been observed.[8-10] Acyclovir does not inhibit hematopoietic recovery after marrow transplantation when compared with a placebo[8]. In our patient, we observed transient erythroblastopenia and leukopenia on the second day of therapy. This may have been related to viral infections or the drug. It is known that viruses commonly causing leukopenia include hepatitis A and B, respiratory syncytial influenza A and B, measles, rubella and varicella. However, in the afore-mentioned infections erythroblastopenia has not been observed to be associated with leukopenia[11-12].

Drug induced neutropenia and leukopenia are not usually associated with an enlarged spleen, segmented or band neutrophils in the peripheral blood or generalized hyperplasia of the bone marrow; this may be an associated transient erythroblastopenia. These changes may be due to either immune-mediated destruction or progenitor failure[13]. We observed a relative increasing number of myelocytes and promyelocytes and an absolute decreasing number of erythroid progenitors in the bone marrow aspiration on the third day of therapy.

The transient erythroblastopenia and leukopenia observed in our patient may be related to the administration of acyclovir. We could not explain this transient hematological change due to any other cause. Fortunately, changes in the hematopoietic tissue were transient but this observation prompted us to monitor the hematological findings during acyclovir therapy.

Summary

A seven-year-old girl with transient leukopenia and erythroblastopenia which developed after the administration of acyclovir is presented. Ayclovir infusion was given in a dose of 5 mg/kg/every eight hours. On the third day of therapy the hemoglobin level fell to 9.9 g/dl, the hematocrit was 26 %, the white blood cell count 4000 percent/mm^3, red blood cells 3.2 million percent/mm^3. Bone marrow aspiration showed a decrease in the number of erythoblasts and a relative increase in the number of promyelocytes and myelocytes. Therapy was discontinued on the fifth day, and on the seventh day the findings were normal including the bone marrow aspiration.

We could not find any other reason which would cause transient erythroblastopenia and leukopenia in our patient.

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