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Severe Hemorrhagic Varicella with Visceral Involvement: Virological and Serological Studies during Treatment with Cytosine Arabinoside

Summary: A boy 13 year-old suffered an extremely severe and prolonged attack of hemorrhagic chickenpox with visceral involvement, the diagnosis being confirmed by isolation of varicella-zoster-virus (VZV). There was no other compromising disease. All preceding vaccinations including two against smallpox had been uneventful. The severity of the attack could not be ascribed to any persistent cellular or humoral immunodeficiency. The patient developed a good antibody response. The course of serological reactions to VZV infection was studied extensively using the different techniques of complement fixation and immunofluorescence for IgG, IgM, and IgA antibodies. Therapy was conducted cautiously using cytosine arabinoside (Ara-C) between the 10th and 17th day of disease; the temperature fell and VZV multiplication ceased, strongly suggesting a beneficial influence on the patient, who recovered completely.

Zusammenfassung: Schwere hämorrhagische Varizellen mit viszeraler Beteiligung: Virologische und serologische Untersuchungen unter Behandlung mit Cytosin-Arabinosid. Ein 13jähriger Bub machte schwerste und prolongierte hämorrhagische Varizellen mit viszeraler Beteiligung durch, wobei die Diagnose durch Isolierung von Varizellen-Zoster-Virus (VZV) gesichert wurde. Es fand sich kein Hinweis für eine konsumierende Grundkrankheit. Alle vorangegangenen Impfungen, darunter zweimal gegen Pocken, waren unauffällig verlaufen. Für die Schwere des Krankheitsbildes konnte weder ein konstanter zellulärer noch humoraler Immundefekt verantwortlich gemacht werden. Der Patient zeigte bei fluoreszenzserologischer Bestimmung der IgG-, IgM- und IgA-Antikörper und in der KBR gute Antikörperbildung. Die Behandlung mit Cytosin-Arabinosid (Ara-C) wurde in vorsichtiger Dosierung zwischen dem 10. und 17. Krankheitstag durchgeführt; Temperaturabfall und Unterbrechung der Virus-Vermehrung sprechen für einen günstigen Effekt des Ara-C auf dieses Krankheitsbild, von dem der Patient sich schließlich vollständig erholt hat.

Complications of chickenpox – such as myocarditis, encephalitis, and pneumonia – are rare but well-known; more often the pediatrician has to deal with a serious, sometimes fatal course of chickenpox or zoster in patients with debilitating diseases, such as leukemia, Hodgkin's disease, or nephrotic syndrome, especially when they are under immunosuppressive therapy.

In 1973 we observed a very severe attack of hemorrhagic varicella with involvement of the lungs, liver, and nervous system, in a patient in whom no compromising disease could be detected.

Case Report

The 13 year-old boy (Ch. D., hospital file No 41.24202.1) had a normal developmental history and no previous serious diseases. At age 5 years he had mumps, at 7 years measles, at 9 years otitis and tonsillitis – in each case without complications. He received no immunosuppressive drugs. Primary vaccination against smallpox in his 1st and revaccination in his 12th year were uneventful; there was also no trouble with other immunizations, namely tetanus, pertussis, diphtheria, and poliomyelitis (Salk and Sabin); he had had no BCG vaccination. The family history was unremarkable; both parents are physicians.

The source of infection was his younger brother who suffered chickenpox without complications. A sister developed varicella at the same time as our patient and showed no complications either.

After an incubation period of 13 days a typical varicella rash appeared without prodromata. On the next day, the temperature rose to 39° C. There were attacks of sharp backache on the 2nd day of illness, followed by paresthesiae of the hands and legs and also ataxia. The rash disseminated very extensively and became hemorrhagic on the 7th day. At this time the lips and eyelids were swollen and the general condition deteriorated, so that the boy was hospitalized on the 9th day.

On admission, there was a severe hemorrhagic varicella rash, with marked involvement of the palms and soles; there were both fresh and older vesicular lesions; the mucous membranes and scalp were widely involved; nasal respiration was impaired. The face was badly distorted by edema of the lips and eyelids (Figure 1). Consciousness was not affected. There was residual ataxia, but no meningitic signs or other neurological symptoms. The lungs were normal on physical examination. The peripheral circulation was adequate. Rectal temperature was 39.5° C. There was neither hepatosplenomegaly, nor jaundice. Chest X-ray revealed bilateral diffuse nodular infiltrations compatible with varicella-pneumonitis.

Gammaglobulin (Intraglobulin®), 1 g i. v., was administered before the results of the serological investigations were available. Antibiotics (carbenicillin, 400 mg/kg daily, and oxacillin, 150 mg/kg daily) were given intravenously for 10 days, although no signs of bacterial infection were evident. Cytosine arabinoside (Ara-C) was given for a total of 7 days (day 10 to day 17), 30 mg/m² daily, as continuous i. v. infusion.

The course of the disease under therapy and on follow up was as follows. The appearance of new crops of varicella ceased at the end of the 11th day of disease. The massive facial edema receded from the 12th day on. The corneae remained intact. The temperature dropped to a lowgrade fever 5 days after onset of therapy. At the same time there was a definite improvement in the patient's general condition. The chest X-ray on the 19th day showed an almost complete recovery of the lung involvement. The patient was discharged in a satisfactory condition on the 33rd day, 23 days after admission.

Received: 28 January 1976

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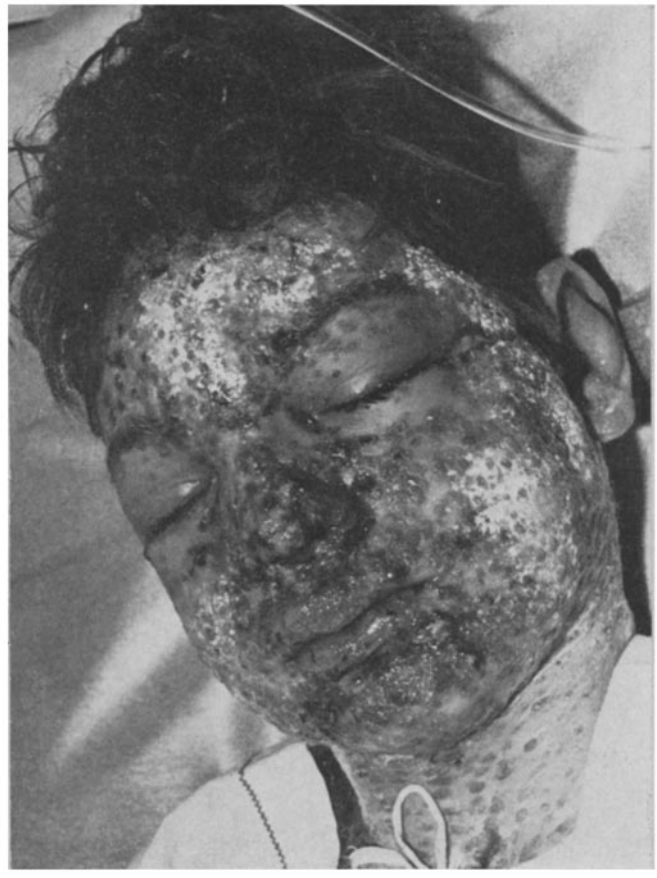

Figure 1: *The patient's face on the 9th day of disease.*

Backache subsided gradually during the next four months; and the boy recovered completely.
Examination after 1 year revealed normal neurological findings. There were various scars on different parts of the body. The face showed discreet scars below skin level without discoloration; the back, on the contrary, showed countless coin-sized scars above skin level without any pigmentation; the anterior chest wall additionally displayed some red-colored, bean-sized scars with keloid formation. There were no scars on the palms, soles, forearms or lower legs.
The laboratory findings are shown in Figure 2. We did not find any evidence of immunosuppression during treatment with Ara-C; the activities of liver enzymes decreased and platelet counts returned to normal within the same period. In the 5th week the response of lymphocytes to PHA-stimulation was found to be normal.
The ECG in the 2nd week showed low voltage and right axis deviation, unusual for the patient's age, which was demonstrated again later. An EEG-tracing on the 32nd day showed no pathological findings.

Virological and Serological Methods

a) *Virus isolation*

Varicella vesicles were opened bloodlessly with a sterile needle. The contents were taken with a platinum-loop and immediately inoculated into full-grown test tube cultures of human embryo lungs fibroblasts (our laboratory strain M29L). Using an immunofluorescent technique the specifity of the CPE was verified by demonstrating typical inclusion bodies in the affected cells. Serum taken from a child with varicella was used as specific positive serum and a pre-varicella serum of the same child as negative control.

b) *Serological studies*

The varicella-zoster-virus complement fixation (VZV-CF) was carried out as a microtest using 4 C' H50-units of complement according to a method which was earlier described for CMV (5). A preparation produced by Behringwerke according to *Krech* was used as antigen.

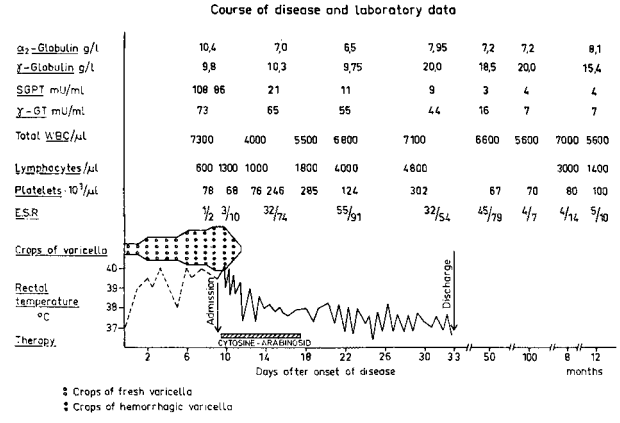

Figure 2: *Course of disease and laboratory data.*

The immunofluorescent method for determining the IgG, IgM, and IgA antibodies was carried out as described for CMV by *Schmitz* and *Haas* (7) as a modification of the *Langerhuysen* method (3). As antigen carriers we used full-grown cell cultures infected with VZV. The antigen preparation is described elsewhere. The patient's own strain and another VZV strain yielded identical results.

Virological and Serological Results

a) *Results of virus isolation*

Table 1 shows the results of the tests for VZV in the skin lesions. Each day we chose several new vesicles from different parts of the body; on admission (9th day after onset of disease) and on the following day, VZV was found in all vesicles — whereas in an ordinary case of varicella VZV is found only during the first 3 to 4 days; the CPE in the fibroblast cultures became visible after 2 to 4 days.

Table 1: *Demonstration of VZV during the course of disease*

Days after onset of varicella-rash	9	10	11	12	13	14	15	16	17	18	20	22	23
Therapy with Ara-C						▬	▬	▬	▬	▬	▬	▬	▬
Isolation of virus (no. of tests/positive)	3/3	3/3	3/3	3/2	3/0	2/0	3/0	2/0	3/0	3/0	2/0	3/0	2/0
No. of days until CPE occurred	3,3, 3	2,3, 4		5,5, 16		17, 17							

On the 11th day VZV was still detectable in all 3 vesicles examined, but the occurrence of CPE was delayed, in one instance up to 16 days after infection of the cell culture. On the 12th day the virus was found in 2 out of 3 vesicles, but not subsequently. Temporally there was a close correlation between the decline and disappearance of VZV and the application of Ara-C to the patient.

b) *Antibody reactions*

Figure 3 shows that there was a considerable antibody reaction. The CF antibody titers reached values of 1 : 512; on the 9th day the test was definitely positive at 1 : 32; it rose rapidly until the 15th day and after 8 months the titer was still high.

The IgG antibody fluorescent test yielded the same course on a higher level; on admission (9th day) a rapid rise had already occurred and a titer of 1 : 2048 was reached; it finally reached 1 : 32,000 and was unchanged after 8 months.

IgM and IgA antibody titers had already reached their highest value by the 9th day (1 : 2048). The IgM antibodies started to decrease steadily during the 3rd week of disease (virus was demonstrable in the vesicles — as mentioned before — up to the 12th day inclusively). After 8 months IgM antibodies were still found, although only in the lowest dilution tested (1 : 8). The IgA antibodies decreased more slowly; after 8 months the titer was still 1 : 32.

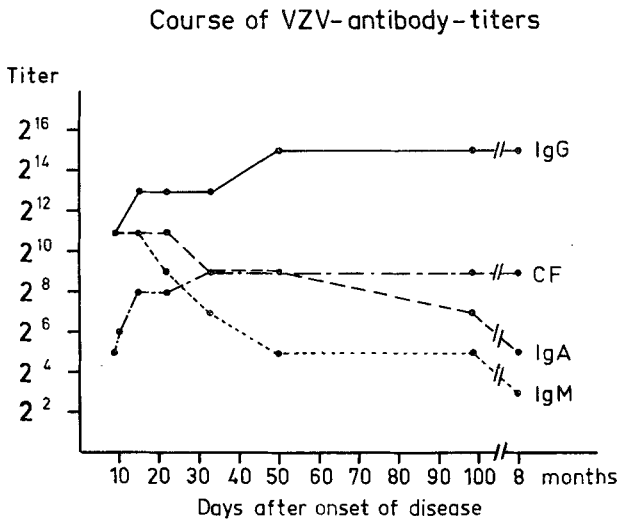

Figure 3: *Course of VZV-antibody-titers.*

Discussion

There are various possible reasons for varicella taking such a serious form; these are, however, not pertinent to our patient:

a) A highly pathogenic strain of virus might be present. The boy, however, was infected within his family and two siblings suffered an uneventful attack of varicella at the same time.

b) The patient might have been affected by underlying disease. But he was apparently not compromised by any other disease before or after the varicella infection.

c) He might have had a defect of humoral immunity: But there was a strong antibody response of normal type.

d) There might be a persistent defect in cellular immunity. However the boy was successfully vaccinated against smallpox in infancy and at the age of 12 years and the PHA stimulation of lymphocytes was normal.

The best we can suggest is a partial mild or transient impairment of cell-mediated immunity, perhaps comparable to that suggested by *J. Gerbeaux* et al. in their report on a 12 year-old girl with a severe attack of a "becegitis" following BCG inoculation (2).

There was a distinct improvement of the patient's condition from the end of 2nd week on. The temperature decreased to about 38° C and finally tapered off to subfebrile values. The laboratory data at that time showed normalization of the platelet count and of the SGPT. The most impressive finding was the lack of evidence of the virus from the 13th day on which was the 3rd day of treatment with Ara-C. The amount of virus had already declined by the 11th and 12th day as judged by the delayed appearance of CPE. The decreasing titer of IgM antibodies during the 3rd week of disease also indicates the interruption of antigen multi-

plication. The IgG and CF antibodies, however, were still increasing at that time.

The dosage schedules for Ara-C in the treatment of herpes virus infections have varied widely between 10 and 100 mg/m² as total daily dose, subdivided into several doses or given as continuous infusion. We preferred a low dose regimen (30 mg/m²/24 hr as continuous infusion after an initial loading dose), because it is assumed that this regimen provides an equal virustatic effect with less cytotoxic side-effects (1). Indeed, we did not note any disturbing side effects of Ara-C: the platelet count which was low before treatment returned to normal during treatment; there was no anemia or neutropenia; the number of lymphocytes and the gamma-globulin in the serum showed a tendency to rise; the SGPT returned to normal; the increased production of specific antibodies took a regular course and was definitely not depressed.

We believe that in this case the coincidence of dramatic clinical improvement with the arrest of virus multiplication shortly after instituting Ara-C treatment indicates a therapeutic effect. Similar favorable experiences have been reported in the literature (6). Cases like ours are rare, and it would hardly be possible to organize controlled therapeutic trials in these patients.

It is important to realize that we have not seen comparable effects with Ara-C on virus multiplication in leukemic children with chickenpox (4). This is in accordance with the results of *Stevens* et al. (8) who could not detect favourable effects of Ara-C in their double-blind trial on patients with disseminated zoster in Hodgkin's disease; in fact, they warn against Ara-C treatment. In Hodgkin's disease, however, the patient is severely immunosuppressed, and it is possible that the cytostatic and immunosuppressive actions of this drug may outweigh the beneficial effects in that situation.

With this study in a case of severe chickenpox we have, for the first time, followed the virological and serological reactions using several techniques. CF proved very sensitive; the titer reached 512, apparently due to the massive and lasting supply of antigen, and was obviously high compared with titers measured in our field trials (4). Titers of this height are rarely seen in children or adults. The immunofluorescent technique was rather more sensitive; the titers of IgG antibodies as well as of CF remained elevated for 8 months. IgM antibodies also reacted very sensitively, and decreased rapidly after the multiplication of virus had ceased but were detectable at low titers after 3 months, although after 8 months they were barely detectable. These findings indicate the superior sensitiveness of the immunofluorescent test and its specificity for the investigation of different types of immunoglobulins.

Acknowledgement

Supported by Deutsche Forschungsgemeinschaft, SFB Medizinische Virologie (31), University of Freiburg (Breisgau).

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