INDUCTION OF SYSTEMIC CANDIDIASIS BY CORTICOSTEROIDS IN ADULT MICE INFECTED NEONATALLY

V. L. Bykov

UDC 616.992.282-036.3-036.65-02:615.357.453]-092.9

Key Words: candidiasis; pathogenesis; corticosteroids

Many clinical observations have shown that administration of corticosteroids (CS) is an important factor contributing to the risk of development of various forms of candidiasis [12, 13]. The stimulating effect of CS on experimental *Candida* infection has been demonstrated in animals infected both parenterally [5] and perorally [1, 2, 11]. In intact mice and rats the mucous membrane of the digestive tract is evidently a highly effective barrier for fungi, which are quickly eliminated from the body [3, 8, 11, 14]. Fungi of the genus *Candida* persist for a long time newborn animals in the digestive tract [1, 4, 10]. The aim of this investigation was to discover the effect of CS on adult animals infected neonatally with *Candida*.

EXPERIMENTAL METHOD

Experiments were carried out on 54 BALB/c mice receiving a suspension of a 2-day culture of *Candida albicans* (strain 2565) in a volume of 20 μl, containing 10^5 blastospores, perorally by means of a micro doser, after which the animals were returned to their mothers. CS (hydrocortisone acetate, 1 mg per animal, subcutaneously on alternate days) was administered for 7-10 days to the neonatally infected animals, on reaching the age of 1.5 months. The following control groups were used: 1) infected mice not receiving CS (12 animals); 2) mice receiving CS but not infected neonatally (eight animals), and 3) adult mice infected perorally with the fungi (dose 10^7 blastospores) and receiving CS 1 month later in accordance with the scheme described above. Material was taken for investigation (organs of the digestive tract, and also the kidneys, liver, heart, and brain) before injection of CS and 2 weeks to 1.5 months after infection, and in the course of 10 days after the beginning of administration of CS. The histologic investigation was conducted on sections of organs stained by the PAS reaction and with hematoxylin. Seedings were taken from the infected organs on Sabouraud's medium, followed by identification of the agent.

EXPERIMENTAL RESULTS

Mice infected neonatally with fungi did not differ in their development from their intact contemporaries. Fungi in the form of separate blastospores and aggregates of them were discovered in the digestive tract 2 weeks to 1.5 months after infection with the agent. They were located in the layer of mucus on the surface of the gastric and intestinal mucosa, without giving rise to invasive lesions. These data confirmed results obtained by the present writer previously [1, 3] and they do not agree with the opinion of Herrera and Guentzel [10], who concluded from a cultural investigation that chronic *Candida* infection may exist in neonatally infected animals. In the course of 7-10 days after the beginning of administration of CS death of the neonatally infected mice occurred, as a result of massive disseminated *Candida* infection involving vitally important organs and systems. Numerous extensive mycotic foci were found in the tissues, with an abundance of elements of pseudomycelium of the fungus. The inflammatory reaction was comparatively mild and irregular, and the exudate contained mainly neutrophilic granulocytes, which were evidently unable to destroy fungi effectively. A study of different parts of the digestive tract showed that the most likely source of dissemination of mycotic infection was the stomach, in which the fungi infiltrate into the mucosa to a considerable depth and penetrate into blood vessels. Development of mycotic lesions was typical in the region of the boundary between

Research Department of Deep Mycoses with Clinical Unit, S. M. Kirov Leningrad Postgraduate Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 109, No. 5, pp. 452-453, May, 1990. Original article submitted June 11, 1987.

0007-4888/90/0005-0597$12.50

the glandular and nonglandular parts of the stomach, in agreement with the observations of Myerowitz [11]. No invasive lesions of the intestine or signs of persorption (penetration of blastospores into blood vessels of the intestinal villi) were observed. Control seedings from infected organs confirmed that the agent was identical with that administered perorally in the neonatal period, thus ruling out the possibility of activation of the endogenous microflora by the action of CS. Injection of CS into uninfected animals and also into mice receiving the fungi in the adult state, did not lead to the development of mycotic infection in any of the control groups.

Infection of newborn animals with fungi of the genus *Candida* thus leads to their long-term preservation in the digestive trait in the form of saprophytes. This experimental model comes closer to the carrier state in man than other models. Injection of CS evidently causes a disturbance of equilibrium in the host — fungus system in favor of the latter. The population of fungal cells increases, blastospores are transformed into germ tubes of the pseudomycelium, and they invade the tissues of the host and subsequently develop disseminated lesions. Consequently, in the model described above, just as in man, exposure to a risk factor for the development of candidiasis (CS) leads to the onset of a mycotic process in the carrier.

The action of CS in inducing candidiasis may be due to several mechanisms. For instance, CS possess a well studied immunodepressive effect [7] which may contribute to the development of invasive lesions and dissemination of the process. It has also been shown that CS enhance the adhesive properties of the epithelium during interaction with fungi [2, 3], and this may have an important role to play in the initial stages of development of the infection. The possibility of a direct stimulating effect of these hormones on fungi likewise cannot be ruled out [9].

LITERATURE CITED

1. V. L. Bykov and Z. O. Karaev, Vestn. Dermatol., No. 2, 21 (1986).
2. V. L. Bykov, Arkh. Patol., No. 4, 45 (1987).
3. V. L. Bykov and E. V. Velichko, Byull. Éksp. Biol. Med., No. 3, 369 (1987).
4. V. L. Bykov and E. V. Velichko, Trudy Leningrad. Nauch. Obshch. Patologoanat., No. 28 (1987).
5. O. K. Khmel'nitskii, The Pathomorphogenesis of Visceral Candidiasis [in Russian], Leningrad (1983).
6. O. K. Khmel'nitskii, R. A. Araviiskii, and O. N. Ekzemplyarov, Candidiasis [in Russian], Leningrad (1984).
7. J. F. Bach and T. B. Strom, The Mode of Action of Immunosuppressive Agents, Amsterdam (1985), pp. 21-104.
8. J. D. Clark, Infect. Immun., **4**, 731 (1971).
9. M. A. Ghannoum, S. Mudher, and G. Burns, Microbios, **42**, 103 (1985).
10. C. Herrera and M. N. Guentzel, Antimicrob. Agents Chemother., **21**, 51 (1982).
11. R. L. Myerowitz, Arch. Path., **105**, 138 (1981).
12. S. Nolting and K. Fegeler, Z. Hautkr., **54**, 58 (1979).
13. F. C. Odds, Candida and Candidosis, Leicester (1979).
14. J. R. Wingard, J. D. Dick, W. G. Merz, et al., Infect. Immun., **29**, 808 (1980).