THE EFFECT OF CHLORTETRACYCLINE ON THE COURSE OF EXPERIMENTAL CANDIDOMYCOSIS OF THE LUNGS IN WHITE RATS

Communication II. Experiments with Preliminary Administration of Chlortetracycline

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In a previous communication [1] we showed that the administration of chlortetracycline to white rats with experimental candidomycosis of the lungs, commenced simultaneously with the introduction of the infection, to some extent aggravates the course of the infectious disease. It remained uncertain whether the duration of administration of this antibiotic affected the course of the candidomycosis. New experiments were carried out to study this aspect of the problem.

EXPERIMENTAL METHOD

As before, the white rats were inoculated intranasally. The technique of histological investigation remained the same.

In the first series of experiments 46 white rats were used, with an average weight of 250 g, and were inoculated with Candida albicans in a dose of 800,000,000 cells; 2 weeks before inoculation, and until the end of the experiment, 23 animals received daily injections of 4000 units of chlortetracycline. The remaining 23 rats acted as controls. Of these animals, 13 died on the first to the third day, and the rest were killed with ether at different times from 3 hours to 35 days after inoculation.

EXPERIMENTAL RESULTS

The lung changes in the 4 experimental and 4 control rats, sacrificed 3 and 5 hours after inoculation, did not differ significantly from those described in the previous experiments. In these animals a fairly considerable number of pneumonic foci was observed, with a predominantly leukocytic exudate, around which were many cells and threads of pseudomycelium of the fungus. The experimental animals did not differ significantly from the controls. In one of the control rats killed after 5 hours, besides Candida cells, small collections of large coccobacilli were seen, partially phagocytized by leukocytes.

Within 14 hours of infection, 3 experimental rats died. Almost the whole extent of the lungs of these rats was occupied by inflammatory foci. Their centers were the alveolar passages, and along the walls of these and also of the small bronchi, there were abundant areas of cell proliferation and pseudomycelium threads of yeastlike fungi. In the 2 experimental and 2 control rats sacrificed at this time, the lung changes were of the same character, but were less widespread, and in the pneumonic foci a more marked cellular (leukocytic and macrophagic) reaction was observed.

On the second day after inoculation 5 experimental and 3 control rats died. The changes in the organs were similar to those present in the animals dying during the first 24 hours. In one control rat, in places in the inflammatory foci groups of small Gram-positive cocci were seen along with proliferating fungus.

In the 6 experimental rats sacrificed on the third to the seventh day, there were fairly extensive areas of consolidation with a predominantly macrophagic exudate. At later periods the formation of granulation tissue was observed, consisting of epithelioid cells, lymphocytes and a few giant cells. In the center of these foci (in the majority of cases) areas could be seen in which the alveoli were filled with disintegrating leukocytes. Among these were a few palely stained yeastlike fungi. In the two killed control rats investigated 3-5 days after inoculation, similar but less widespread changes were

observed. In the two rats which died at the same time, spontaneous and severe inflammatory changes were found in the lungs and pleural cavities, presumably connected mainly with the coccal microflora. In the 2 control rats sacrificed on the seventh day after inoculation there were only comparatively few areas of consolidation, in which the alveoli contained epithelioid cells, macrophages and lymphocytes. In one of these, abscesses were also found, caused by the cocci.

On the 10th-15th day after inoculation, fairly widespread foci of consolidation were found in the lungs of both sacrificed experimental rats, formed by proliferation of granulation tissue with the structure described above. Within these foci were cavities containing disintegrating leukocytes, cells and threads of the pseudomycelium of Candida, mostly Gram-negative. The same foci, although less often, were found in the two rats sacrificed on the 26th and 35th days. In the control animals these changes were less pronounced. They were present in only 5 of the 8 rats sacrificed on the 10th-35th day after inoculation. Under these circumstances small abscesses, associated with fungi, were present in these foci in only one of the animals. In 5 animals large abscesses and,sometimes,bronchiectases were found, mainly caused by cocci. Besides these microorganisms, a few palely stained yeastlike fungi could be found in the abscesses.

The results of a quantitative mycological investigation of the anterior lobe of the right lung, carried out by N. A. Zaikina (Leningrad Institute of Antibiotics) agreed on the whole with the results of the pathologoanatomical study. Only in 6 animals with proliferation of granulation tissue–among which were abscesses containing Gram-negative yeast cells–were no positive Candida cultures obtained.

The prolonged administration of chlortetracycline thus evidently aggravated the course of experimental candidiasis of the lungs in white rats to a slightly greater degree than when administration of the antibiotic began simultaneously with inoculation. This is shown by the higher mortality, the more widespread nature of the foci in the experimental animals and the more frequent discovery of fungi in these foci.

The presence of severe spontaneous infections of the lungs by a bacterial flora in a proportion of the control animals complicated the evaluation of the effect of preliminary administration of chlortetracycline. In this connection a supplementary series of experiments was carried out in which 36 white rats were inoculated (with 1,000,000 Candida albicans cells).

Since, when the experiment was performed in this manner, changes were observed in the lungs for a very short time, the investigation lasted only the first 3 days. In this way the animals could be divided into several groups in which the duration of chlortetracycline administration differed. The daily dose of the antibiotic was 4000 units. All the animals were killed with ether.

In one of the 11 control rats killed 30 minutes after infection, solitary cells and (more rarely) small groups of yeastlike fungi were found in the bronchi. After 3 and 5 hours (4 rats) no free fungus cells were present in the bronchi, bronchioles and alveolar passages. Only a few macrophages, with protoplasm filled with yeast cells, were to be found here. Perivascular and peribronchial collections of leukocytes were often found. From 1 to 3 days after inoculation, macrophages with red protoplasm (when stained by Shabadash's method) were found in the lumen of the bronchi in all 6 animals. This suggested that in the protoplasm of these macrophages there were remains of lyzed fungi. In one of these rats, during the first day, isolated pin-point foci of leukocytes and macrophages were found, but no yeastlike fungi were present in them.

In 3 of the 13 rats receiving chlortetracycline throughout the experiment from 2 weeks before inoculation, the changes found 30 minutes and 3 hours after inoculation,respectively, were similar to those present in the control animals. Later, a definite difference could be observed. For instance, in one of the 2 rats sacrificed after 5 hours, a small pneumonic focus was found, with an exudate containing mainly disintegrating leukocytes. Yeastlike fungi were seen among these leukocytes. More extensive changes were observed in one rat sacrificed 24 hours after inoculation, in which comparatively numerous foci of consolidation were found, with an exudate of leukocytes and macrophages, situated mainly in the region of the alveolar passages. In these foci cells and short threads of Candida pseudomycelium were comparatively numerous. In the remaining 7 rats, sacrificed 1-3 days after inoculation, a large number of macrophages could be seen, with red protoplasm (when stained by Shabadash's method) in the bronchi and lung tissue – more than in the rats of the control group.

The lung changes which developed in animals receiving chlortetracycline only during the 2 weeks before inoculation with Candida culture (6 rats) or only after inoculation (6 rats) were more marked than in the control animals, but less so than in the rats receiving chlortetracycline throughout the experiment.

SUMMARY

The results are presented of pathologicoanatomical investigations conducted on 82 white rats infected intranasally with a Candida albicans culture.

Pulmonary candidiasis developed when the animals were infected with 800 million Candida cells. The mortality rate in animals to which chlortetracycline was administered for a period of two weeks prior to infection, and after it,was higher than in controls and in those animals to which chlortetracycline was given simultaneously with the infection.

Candidiasis failed to develop in infection with one million Candida cells. However, in preliminary (especially prolonged) chlortetracycline administration, multiplication of the fungi occurred with formation of inflammatory foci.

Thus, prolonged preliminary chlortetracycline treatment contributes to the development of experimental candidiasis to a greater degree than when the preparation is administered simultaneously with the infection.

LITERATURE CITED

1. A. V. Tsinzerling, Byull. Éksp. Biol. i Med. 47, 6, 33 (1959).*

*Original Russian pagination. See C.B. translation.