Tick-Borne Typhus Fever of Northern Asia: Some Characteristics of the Pathogenesis

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Morphological changes in the viscera of albino mice were studied over the course of North Asia typhus fever. In general, the microcirculatory bed in the studied organs (brain, liver, spleen, peritoneum, and testicle) corresponded to angioparalytical capillary and venular hyperemia. Macrophagic reaction (proliferation of stellate macrophages) transformed into granulomatous reaction in the course of the experiment. Macrophagic reaction of the spleen was characterized by blurred follicular pattern. In the testes a tendency to the loss of normal spermatogenesis was observed.

Key Words: *rickettsia; macrophagal reaction; granuloma; spermatogenesis*

Experimental modeling of a disease in laboratory animals demonstrates its development, which is particularly important for investigation of severe human infections, *e.g.* rickettsiosis. Studies of experimental rickettsial infections are carried out for isolation of strains and for evaluation of biological, morphological, and immunological characteristics of rickettsia and their identification [1,3,7,9].

Here we studied some features of pathogenesis of the North Asian typhus fever (TF) on the basis of pathomorphological changes in the viscera of laboratory animals infected with TF agent.

Today TF is regarded as a returning infection, whose incidence increased more than 6-fold since 1979 [8].

It is noteworthy that *Rickettsia sibirica* strains isolated since the 1940s are genetically homogenous and differ only by their virulence [5,6].

MATERIALS AND METHODS

Experiments were carried out on random-bred albino mice (12 g). The animals were infected intraperitoneally with 1.0 ml of 10% suspension of chick embryo yolk sack infected with *R. sibirica* (strain Netsvetaev). Strain Netsvetaev is a neotype of *R. sibirica* isolated in 1946 from the blood of a patient in the Altai region. Biological characteristics of this strain in general reflect the characteristics of the majority of isolated and studied *R. sibirica* strains in the entire region of natural foci of this disease, except the Primorye territory [6].

Control mice (n=10) were injected intraperitoneally with 1 ml normal saline. The animals were decapitated under narcosis on days 4, 6, and 8 postinfection and autopsied.

RESULTS

The first clinical signs of the disease (dim ruffled fur, dyspnea, loss of appetite, *etc.*) were observed several hours postinfection. All animals infected with *R. sibirica* died on days 1-8 postinfection. The effect of rickettsial toxin on mice is angioparalytical, *i.e.* it disturbs cerebral circulation, which culminates in diffuse capillary stasis, the direct cause of animal death on day 1 after inoculation [1].

Hemodynamic disorders of the microcirculatory bed, paresis and plethora with sludge reaction predominated in the pia mater and brain tissue on day 4 postinoculation. Edema and small cavities around reduced capillaries were detected (Fig. 1). On day 6

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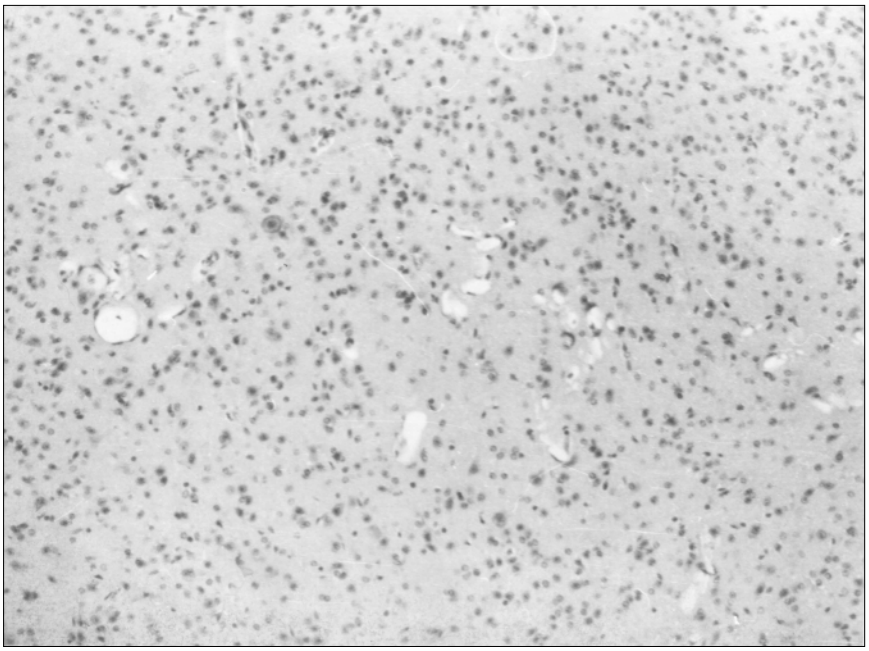

Fig. 1. Mouse brain on day 4 after infection with typhus fever agent. Hematoxylin and eosin staining, ×32. Cavities of different size at sites of capillary ectasia.

postinoculation these capillary changes were supplemented by lymphohistiocytic focal proliferation with the first segmented leukocytes under the pia mater. On day 8 capillary paresis in the brain and cerebellum somewhat decreased, perivascular edema persisted.

Hemodynamic changes in the liver (ectasia of central veins, plethora of portal vessels, and extension of the sinusoidal network) were detected on day 4 postinfection. Lobular structure of the liver was preserved, parietal segmented leukocytes and large macrophagal cells appeared. Proliferative reaction of stellate reticuloendotheliocytes was paralleled by the formation of numerous granulomas consisting of reticuloendothelial cells, small fibroblasts, and small lymphocytes. On day 6 the granulomatous process became less active (the number and size of granulomas decreased and they became more compact because of accumulation of small fibroblasts). Sites with more pronounced lymphohistiocytic proliferation appeared in the portal tracts and penetrated into lobules through damaged terminal plate. This corresponds to the picture of aggressive hepatitis with severe dystrophy and death of individual hepatocytes (Fig. 2). On day 8 pronounced dystrophy of the hepatocyte cytoplasm around the central veins was seen, while portal tracts were surrounded by normal hepatocytes. The sinusoidal network was narrow, stellate reticuloendotheliocytes did not proliferate.

In the spleen, moderate hyperplasia of the red pulp and its predominance over the white pulp were noted on day 4 postinfection. Follicles had blurred unclear boundaries. On day 6 the follicle lost their boundaries due to enlargement of the red pulp; polynuclear macrophages concentrated in the subcapsular zone. On day 8 the spleen almost completely lost follicular pattern because of total hyperplasia of the red pulp. The number of polynuclear macrophages markedly decreased.

The peritoneum on days 4-6 was presented by loosely connected muscular bundles and connective tissue with plethoric vessels. The inflammatory process spread in the interstitium among muscular bundles and took a chronic course. On day 8 postinfection signs of myositis persisted in the peritoneal interstitium.

Testicular tissue on days 4-6 looked mosaic depending on its distance from the capsule. In the central zones the seminal tubules were densely packed and had signs of manifest spermatogonial hyperplasia and hypersecretion. Death of Sertoli cells and protrusion of the capsule at sites of their death were seen. The maximum changes in the tubules were seen near the capsule, *i. e.* near foci of leukocytic infiltration. Rare flagellated spermatocytes were seen in epididymis. On day 8 postinfection all the tubules looked loose, with dilated lumens. The capsules were dilated along the entire length. The number of spermatogonia decreased and their layer was loose; numerous abnormal polynuclear spermatocytes were seen in the tubules, but no typical flagellated cells. Only solitary dystrophic polynuclear spermatocytes were seen in the epididymis, while mature male sex cells were virtually absent (Fig. 3).

Hence, pathomorphological changes in TF are characterized by vascular disorders and involvement of monocyte-macrophages into the pathological process, which is one of the most universal components of inflammation. By day 4 postinfection the disease was clinically manifest, the entire picture of micro-

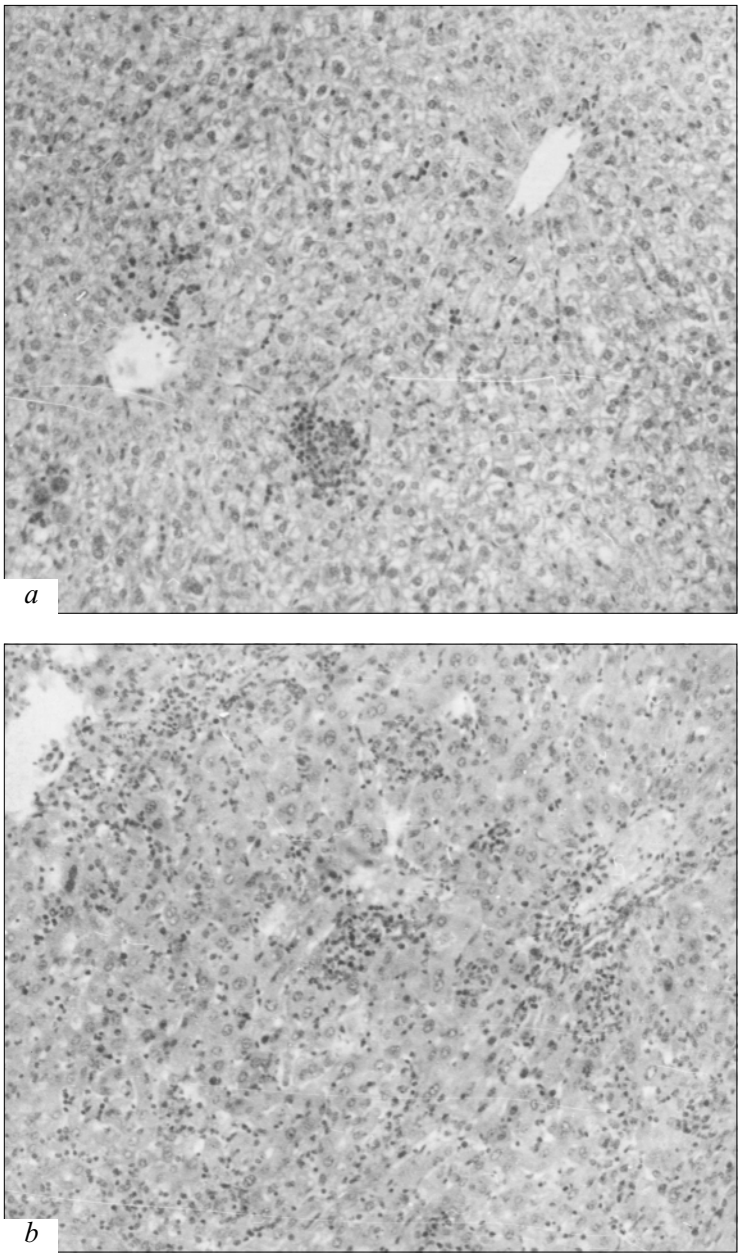

Fig. 2. Mouse liver on day 6 after infection with typhus fever agent. Hematoxylin and eosin staining, ×32. *a*) solitary compact granulomas; *b*) diffuse lymphohistiocytic infiltration of portal tracts spreading through the terminal plate.

circulatory bed of the pia mater, brain matter, liver, spleen, peritoneum, and testicle corresponded to angioparalytical capillary and venular hyperemia. Angioparetic effect of rickettsial toxin manifested in circulatory disorders in the brain, edema, formation of small cavities around reduced capillaries, and culminated in capillary stasis and vasodilatation, which became the main cause of animal death. A general trend of endotheliocyte proliferation in capillaries and the adjacent pericytes in the cerebral cortex was detected. Endovasculitis was observed at the end of the experiment.

Macrophagic reaction (proliferation of stellate macrophages) is transformed into granulomatous reaction. The presence of granulomas in the liver and their absence in other organs can be explained by the route of infection. The liver becomes the target organ under these conditions, and we successively observed the involvement of the terminal plate, aggressive hepatitis with severe dystrophy and death of individual hepatocytes.

Macrophagal reaction of the spleen was characterized by concentration of polynuclear macrophages in the subcapsular zone and blurred follicular pattern because of red pulp hyperplasia. A general tendency to the loss of normal spermatogenesis with the appearance of numerous giant spermatocytes was observed by the end of the experiment. This phenomenon was reported for epithelial cells (not spermatocytes) during viral infection (*e. g.* cytomegalovirus, herpes

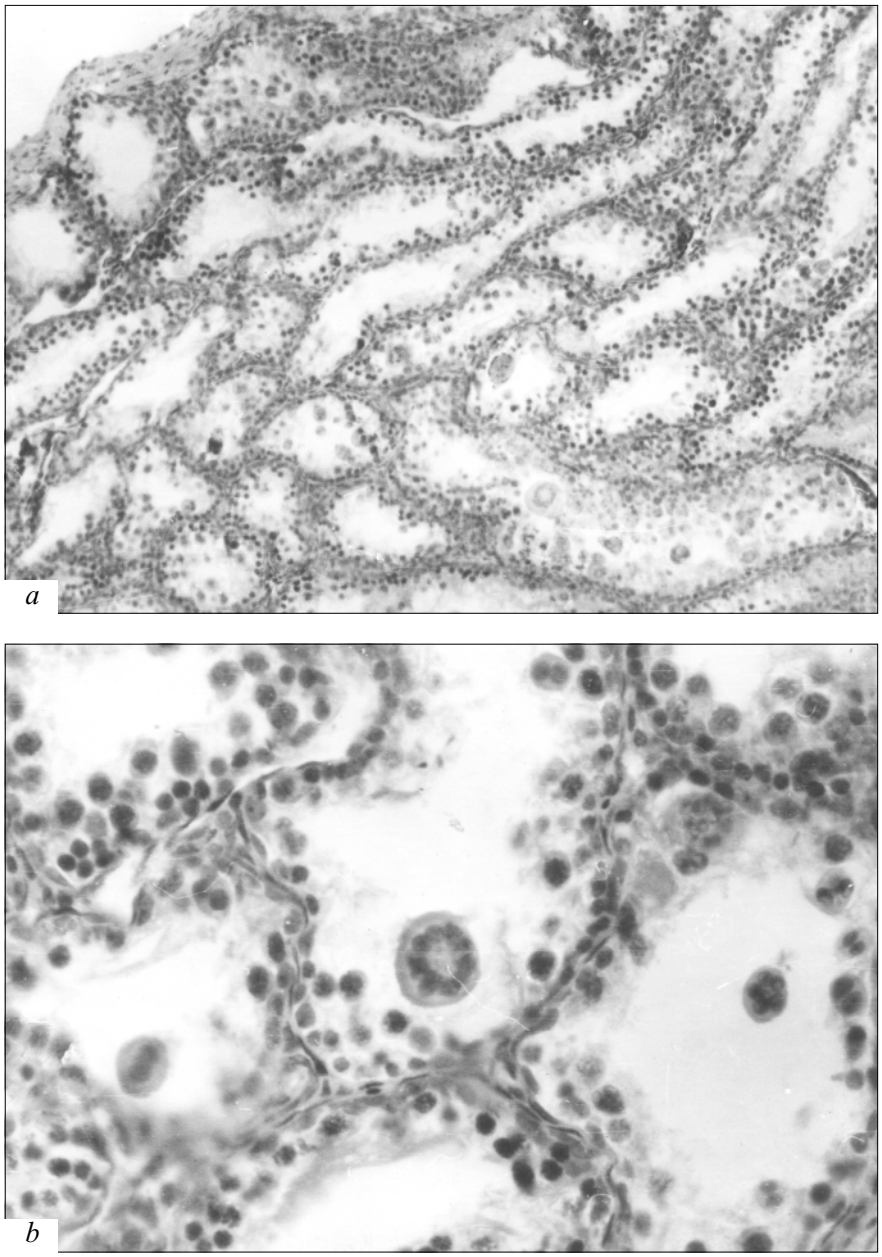

Fig. 3. Mouse testicular seminal tubules on day 8 after infection with typhus fever agent. Hematoxylin and eosin staining. *a*) tubular ectasia with uneven proliferation of spermatogenic cells, ×120; *b*) appearance of atypical multinuclear spermatocytes in tubules, hematoxylin and eosin staining, ×400.

simplex virus, *etc.*). This is associated with some clinical parallels, such as suppression of spermatogenesis in humans with a history of typhus fever, which makes studies in this sphere very actual.

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