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RESULTS OF INTRAVASCULAR IMPLANTATION OF METHOTREXATE-SATURATED EMBOLI

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Inadequately researched methods of treatment of malignant neoplasms demand the study of new therapeutic approaches to the solution of this problem. The efficacy of targeted local application of cytostatics directly into the tissue of a neoplasm has been the subject of numerous trials. Solutions of cytostatics for this purpose are injected into an artery supplying blood to the tumor tissue [6], or endolymphatic introduction of cytostatics has been used [4]. All methods of targeted administration of cytostatics into tumor tissue so far tested have been distinguished by short term action of the drug, and accordingly, in order to achieve a definite therapeutic effect, they usually have to be given repeatedly. If cytostatics are administered by these methods, just as when given in the normal way, without targeting, they give rise to marked toxic effects on hematopoiesis, the gastrointestinal tract, and other organs, making the patient's state serious [5]. It is also irrational to administer expensive therapeutic preparations by these methods.

The idea of targeted local administration of cytostatics by occluding the blood vessels of the tumor by emboli containing a therapeutic substance which would not pass through the blood vessels or lymphatics of the tumor but which would remain in it for a longer time, thus prolonging its cytostatic action, is attractive. The procedure would also inhibit growth of the tumor and would reduce its blood supply. Sufficient experience has now been obtained of the practical use of hydrogel emboli, based on polyhydroxyethylmethacrylate, for endovascular occlusion of blood vessels in a wide range of human diseases [1, 3]. Of all the emboli at present known, those from hydrogel have been found to be therapeutically optimal.

The aim of this investigation was to discover if hydrogel emboli can be saturated with methotrexate, a widely used cytostatic [5], and to study the character of histological changes in the vessel wall and surrounding tissue after endovascular implantation of the emboli.

EXPERIMENTAL METHOD

Synthesis of spherical particles based on poly-2-hydroxyethylmethacrylate has been described previously [7]. Hydrogel particles measuring 0.4-0.6 mm, washed to remove unreacted monomer, were activated in dioxan by means of *p*-nitrophenylchlorformate at 4°C for 4 h. After removal of the nitrophenol formed in this way from the hydrogel, activated hydrogel was reacted with hexamethylenediamine at room temperature for 8 h. The washed hydrogel, modified by the diamine, was added to a saturated aqueous solution of methotrexate, which was completely adsorbed on the polymer matrix.

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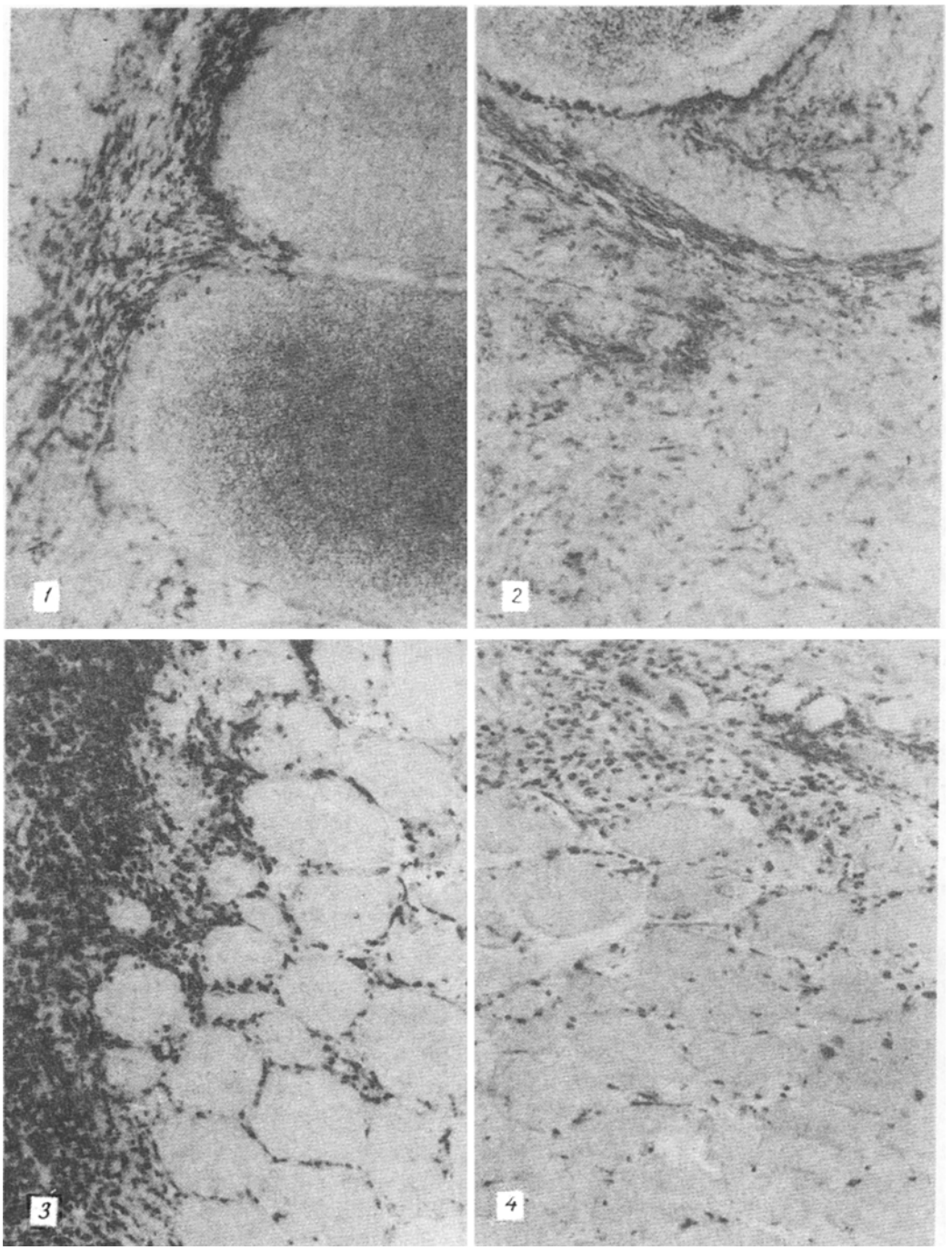

Fig. 1. Two hydrogel emboli saturated with methotrexate in lumen of rabbit femoral artery. Intima and muscular coat of artery are absent. Material of emboli adjacent to adventitia of vessel. Small focus of muscular coat still remains in angle between two emboli. Penetration of cells into pores of emboli not present. Seven days after implantation of emboli. Hematoxylin and eosin. 160×.

Fig. 2. Fragment of artery whose lumen contains hydrogel embolus saturated with methotrexate. Intima and media necrotic. Sclerosis of tissue of perivascular space. Period of implantation 14 days. Hematoxylin and eosin. 160×.

Fig. 3. Necrosis of skeletal muscle fibers with demarcation inflammation, lying in immediate vicinity of site of intraarterial implantation of emboli saturated with methotrexate. Hematoxylin and eosin. Seven days after implantation.

Fig. 4. Necrosis and beginning of regeneration of skeletal muscle fibers in zone immediately adjacent to site of endovascular implantation of emboli saturated with methotrexate. Fourteen days after implantation. Van Gieson's stain 160×.

Emboli thus prepared, after appropriate sterilization, were implanted into the femoral artery of a rabbit. A histological study of vessels containing emboli and their surrounding tissue was carried out 7 and 14 days after implantation. Histological sections were stained with hematoxylin and eosin and by Van Gieson's method. Vessels with surrounding tissues containing hydrogel emboli without methotrexate served as the control.

EXPERIMENTAL RESULTS

The control experiments showed virtually no reaction of the vascular wall. Only stretching was observed, in the case of tightly packed emboli [2]. After implantation of emboli with methotrexate, necrosis of the intima and total or partial necrosis of the muscular coat of the artery were observed, so that after 7 and 14 days the embolus in the histological section was in direct contact with the adventitia (Figs. 1 and 2). Necrosis, followed by signs of regeneration, were observed in the skeletal muscles surrounding the vessel in the early period of the investigation (Figs. 3 and 4). With lengthening of the time of observation, the necrotic muscle fibers were absorbed and regeneration activated. Lysis and regeneration of muscle tissue were observed first of all in the region close to the blood vessel containing emboli with methotrexate. The emboli themselves 7 days after implantation appeared to have small pores, which were empty or contained fibroblasts penetrating into them, and increasing in number with lengthening of the period of observation. The results indicate that binding of methotrexate with the material of the embolus is weak and that it diffuses into the vessel wall, damaging it, after which it passes through the damaged wall into the surrounding tissue, which it also damages. Necrosis of the vascular wall and necrosis of the skeletal muscles were mentioned above. Invasion of the pores of the hydrogel by fibroblasts on the 7th and, in particular, the 14th days after implantation is an interesting fact. This may indicate sufficiently complete release of the cytostatic at that moment from the material of the embolus, which does not create a local toxic effect, which could prevent invasion of connective tissue cells into the pores of the hydrogel.

It can thus be concluded from these results that hydrogel emboli can be saturated, in principle, by adsorption with methotrexate, one of the most widely used cytostatics, and also that this drug can diffuse for several days from embolic material, to exert its corresponding biological action on the surrounding tissue. The creation of a new product with targeted and prolonged therapeutic action would seem to be promising.

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