THE EFFECT OF PNEUMOTHORAX ON METASTASIZATION OF A BROWN-PEARCE TUMOR IN THE LUNGS OF THE RABBIT

V. D. Vinogradova

Pathophysiological Laboratory (Head – Candidate Med. Sci. I. P. Tereshchenko) of the P. A. Gertsen State Oncological Institute (Dir. – Prof. A. N. Novikov, Scientific Director – Active Member AMN SSSR Honored Scientist Prof. A. I. Savitskii), Moscow

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Experimental researches conducted in A. D. Speranskii's laboratories have shown that the course of metastasization is dependent upon the place and time of application of a superimposed nerve injury and also on the character of such an injury [6, 7, 8, 13, 16-19]. By changing the trophic state of the tissue in the corresponding organs, these factors create conditions favoring the development or nondevelopment of metastases.

Our work was undertaken in accordance with the planned further development of these researches. We studied the role of changes in the functional state of the lungs in the process of metastasis-formation, on the assumption that a change in the functional state leads to corresponding trophic changes and, hence, to changes in the growth of the tumor.

In the accessible literature, both Soviet and non-Soviet, we found no work on the study of metastasization in the lungs under different functional conditions.

METHODS

The present investigation was conducted on 102 male rabbits weighing 2.0-2.5 kg, inoculated with a Brown-Pierce carcinoma. In experimental oncology it is known that the highest proportion of successful inoculations and of metastasization in the internal organs is given by intratesticular transplantation of a Brown-Pearce carcinoma [2, 11, 15, 21, 23]. For this reason, for the study of the metastasization of this tumor in the lungs we used intratesticular transplantation. The changes in the functional state of the lungs were brought about by the induction of a unilateral artificial pneumothorax.

We conducted two series of experiments. In the first series 82 rabbits were used, 42 experimental and 40 control animals. The experimental rabbits underwent induction of an artificial tension pneumothorax on the right side. For this purpose 75 cc of air was introduced into the pleural cavity by means of a Kachkachev apparatus. One hour after induction of the penumothorax, a Brown-Pearce tumor was transplanted into the left testicle of all the rabbits (experimental and control) in a dose of 0.5 ml of a 20% tumor emulsion. Throughout the subsequent duration of the experiment, four insufflations of air were given into the right pleural cavity of each experimental rabbit, in volumes of 75 cc at intervals of 5 days, in order to maintain the lung in a collapsed condition. On the 26th day of the experiment all the rabbits were sacrificed and autopsied in order to study the process of metastasis formation. The development of metastases was determined in accordance with the presence of tumor nodules visible to the naked eye. Metastasization was studied in the mesentery and the serous membrane of the large and small intestine, the parietal peritoneum, the diaphragm omentum, kidneys, adrenals, liver, and lungs. For convenience of comparison of the degree of metastasization in the various organs of the

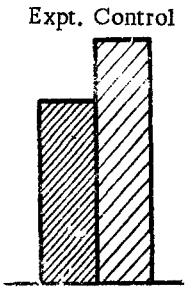

Fig. 1. Degree of involvement of organs by metastases of a Brown-Pearce tumor. Closely shaded part – degree of metastasization in the pneumothorax experiment; lightly shaded part – degree of metastasization in controls.

Fig. 2. Distribution of metastases of a Brown-Pearce tumor in the lungs after induction of an artificial tension pneumothorax on the right side.

experimental and control animals, we used a conventional numerical notation for the metastases in accordance with their size and number. As regards size: small – under 0.2 cm, average – from 0.2 to 0.5 cm and large – over 0.5 cm; as regards number: few – under ten, average – from 10 to 30, and multiple – over 30. The conventional numerical notation was as follows: few small metastases were denoted by 1 point, an average number of small metastases – 2, multiple small metastases – 3 points; few average-sized metastases – 2 points, an average number of average-sized metastases – 4 points and multiple average-sized metastases – 6 points; few large metastases were denoted by 3 points, an average number of large metastases – 6 and multiple large metastases by 9 points. We then added together the figures of metastasization thus obtained organ by organ, and deduced the mean indices calculated in terms of one rabbit. In this way we constructed the diagrams which are reproduced below. Our results were treated statistically by the method of probability of the presence of a correlation by calculation of the coefficient of association χ^2. This method serves to determine the adequacy and the reliability of the experimental material.

The second series of experiments was undertaken in order to exclude the possibility of inequality in the accumulation of tumor cells in the normal and collapsed lung. For this purpose we transplanted equal volumes of Brown-Pearce tumor emulsion simultaneously into the right and left lungs, and then induced a unilateral artificial pneumothorax.

We carried out the simultaneous transplantation of Brown-Pearce tumor into the lungs of 20 rabbits, in a dose of 0.3 ml of 20% tumor emulsion in each lung. The transplantation was done as follows: along the course of the seventh rib, in the right and left axillary regions, skin incisions 2 cm long were made. The subcutaneous tissues, the latissinus dorsi and serratus muscles were divided on both sides and the thorax was exposed. Along the outer edge of the longissinus dorsi muscle, in the seventh intercostal space, a needle was introduced on each side to a depth of about 0.4 cm. The tumor suspension of Borwn-Pearce rabbit carcinoma was carefully inoculated beneath the visceral pleura.

An artificial pneumothorax was immediately induced on the right side in 13 rabbits by introduction of 75 cc of air into the pleural cavity. The left lung, with no pneumothorax, acted as a control. The remaining seven rabbits were controls. Five days after induction of the artificial pneumothorax, 75 cc of air was insufflated into the right pleural cavity of the experimental rabbits. Ten days after transplantation of the tumor, both experimental and control animals were sacrificed, autopsied and the lungs carefully examined.

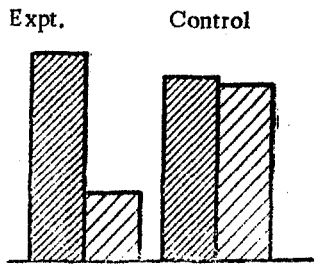

Fig. 3. Degree of metastasization of a Brown-Pearce tumor in the lungs. a) Experiment; b) controls. Closely shaded part – metastasization in the left lung; lightly shaded part – metastasization in the right lung. The columns represent the mean indices of metastasization in the lung for each group and are calculated in terms of one animal.

RESULTS

In the first series of experiments with intratesticular implantation of the Brown-Pearce tumor, the transplantation was successful in 79 rabbits. In two rabbits of the experimental group and one of the control group the tumor did not take. In the experimental group metastasis formation took place in 39 of 40 rabbits, and in the control group, in 35 of 39 rabbits. Differences were observed in the metastasis formation between the experimental and control animals: in the rabbits of the experimental group the degree of metastasization in the organs was less than in the controls (Fig. 1). The difference in metastasization was statistically significant. The value of $\chi^2 = 25.95$ and $\eta = 5$. On the basis of Fisher's χ^2 table, P for these values is considerably smaller than 0.01. Consequently, the change in the functional state of the lung as a result of the induction of an artificial tension pneumothorax brings about a decrease in the degree of metastasization in the organ.

Metastases were present in the lungs in 20 of the 39 rabbits in the experimental group. A distinctive feature of their distribution was that the left lung was more severely affected by metastases (the metastases in the lung were both larger and more numerous) than the right, collapsed lung (Fig. 2). In the control group metastases in the lungs were observed in 16 of 35 rabbits. Their distribution by number and size was the same in both lungs. It will be clear from Fig. 3 that the degree of metastasization in the lung affected by the pneumothorax was only 40% as high as that in the opposite lung. The difference in the degree of metastasization is statistically significant. The value of $\chi^2 = 19.73$, $\eta = 5$. The probability P corresponding to these values is much less than 0.01.

The study of the development of metastases in the lungs when the functional state of one of them is modified by the induction of an artificial tension pneumothorax thus revealed a weaker development of metastases in the collapsed lung.

In the second series of experiments with transplantation of a Brown-Pearce tumor in both lungs, in all 13 experimental animals the development of a tumor was observed in the left lung, whereas in the right lung the tumor completely failed to develop in 4 rabbits, in 7 it was much smaller than in the left, in one rabbit the tumor was the same size in both lungs and only in one rabbit was the tumor in the right lung significantly larger than in the left. In the control animals tumors developed in both lungs and in 6 rabbits they were perfectly identical in size. Only in one case was the tumor in the left lung significantly larger than that in the right. Thus in the overwhelming majority of animals, the tumor developed more rarely in the right lung and grew more slowly than in the left lung, which was not affected by pneumothorax, in spite of the fact that an equal volume of tumor cells was introduced into the two lungs.

It is impossible to explain the weaker development of metastases in the collapsed lung by the possibility of the mechanical effect of tissue compression. Admittedly, it has been considered until recently that the filling of the pleural cavity with air places the lung in a state of compression and completely or partially excludes it from the function of respiration. Modern physiological and clinical findings do not fit in with the old ideas of the biomechanics of the lungs in pneumothorax. Work by several authors [1, 3, 4, 5, 9, 10, 14, 20, 22] has shown that, after the induction of an artificial pneumothorax, the ventilation of the lungs is not diminished but increased and the compressed lung accomplishes considerable respiratory excursions.

G. E. Platonov [12] has shown that after induction of an artificial pneumothorax the cell respiration in the collapsed lung is intensified, with an increase in the catalase, and, to a lesser degree of the peroxidase activity and a moderate increase in glycolysis. The increase in the oxidative processes leads to activation of bacteriolysis and phagocytosis.

From the foregoing remarks we may postulate that unfavorable conditions for the development of metastases and also for developement of the primary tumor are created in the lung when it is in a state of collapse as a result

of the induction of a pneumothorax, in consequence of changes in its biological functions and in its associated metabolic processes. Furthermore, the change in the functional activity of the lung must inevitably lead to some degree of modification of the general metabolism of the body, which in turn may be responsible for the diminution of the degree of metastasization in various organs. This factor may be associated with changes in the resistance to growth of tumors.

These results are evidence of the important role of the functional state of organs in the process of metastasization.

SUMMARY

Studies of the development of metastases in the lungs after changes in the functional state of one lung caused by induction of an artificial pneumothorax, demonstrated a less pronounced development of metastases in the collapsed lung and reduction of metastasization into organs. The data obtained point to the important role played by the functional condition of organs in the process of metastasization.

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