RESORPTION OF UNTREATED METASTASES AFTER SUBJECTION OF RABBIT BROWN-PEARCE TUMORS TO HIGH-INTENSITY ULTRASONIC WAVES

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In communications from our laboratory we have reported that Brown-Pearce tumors in rabbits were made to resorb after being subjected to high-intensity ultrasonic waves [1]. Histological examination of the tumors immediately following their treatment with ultrasonics did not indicate any evidence of morphological alterations. However, the survival capacity of the tumor cells is markedly diminished. This is manifested by the sharp decrease in the multiplication of the tumor cells and the development of dystrophic processes in the tumor tissue. This progressive dystrophy of the tumor cells leads to their total regression. The tumor either becomes resorbed tracelessly or is replaced by scar, or else loses all distinguishing features and becomes encapsulated.

The examination of the untreated metastases and the study of the changes going on in them while the primary tumor which had been subjected to ultrasonic waves is undergoing regression, presents a topic of the greatest interest. This communication is devoted to an examination of this subject.

In our experiments we used transplants of the Brown-Pearce tumor which is characterized by intensive and swift metastases, so that castration 1 to 6 hours after introduction of the tumor material does not prevent metastatic spread [3, 4]. When we used the classical procedure of inoculating the tumor material into the testicle, we found ourselves in agreement with other workers in stating that in only 6 to 8% of the total could spontaneous tumor regression be observed. However, the method of inoculation used is important in determining the frequency of metastases to the inner organs and the percentage of spontaneously regressing tumors. Thus, when the tumor material was introduced intramuscularly, in our experiments 27.3% of the cases showed spontaneous resorption of the swellings.

EXPERIMENTAL METHODS

Our experimental group included 23 rabbits: a control group – 12 which had manifested spontaneous resorption of the primary tumor nodule, isolated from 112 rabbits which had been injected intramuscularly and intratesticularly with Brown-Pearce material; and an experimental group of 11 having both tumor and metastases which were observed for indications of tumor recession after various regimens of ultrasonic treatments.

The Brown-Pearce tumor was given to both the control and further experimental group of rabbits intramuscularly and intratesticularly. The tumor tissue was pulverized, suspended in saline solution (1 : 3) and injected in the amount of 0.8 to 1 cc. To facilitate the application of ultrasonic waves, the testicle was displaced under the skin on the forward surface of the thigh and fixed in place with a stitch. A similar operation was performed on the control rabbits. The animals received ultrasonic treatments from the powerful installation built by A. K. Burov [2]. The treatment of the tumor nodules was conducted after the method of G. D. Andreevskaya on the 7 to 11th day after the tumor inoculation, i. e., at a time when metastasis has occurred and when macroscopic evidence of numerous metastatic nodules can be seen on autopsy.

The method of application was as follows: contact was established through vaseline and with sound waves conducted through the liquid medium of water. The treatment regimen: frequency of 750-1500 kilocycles; power of 27-150 W/cm^2; exposure 1.3-75 seconds.

The experimental and control groups were examined carefully each week. The animals which died or were sacrificed at the end of the experiment were examined thoroughly on autopsy. The rabbits were observed from a period of several months (3 to 4) up to 3$^1/_2$ years.

EXPERIMENTAL RESULTS

In our studies we observed spontaneous regression of the primary tumor only in those rabbits which were still free of metastases. In these animals we were never able to see or palpate metastases. This absence of metastasis was also confirmed by subsequent autopsies as was the absence of any scars or calcifications within the internal organs and lymph nodes. We also failed to uncover any reports in the literature of the spontaneous regression of a primary growth due to Brown-Pearce tumor and metastases.

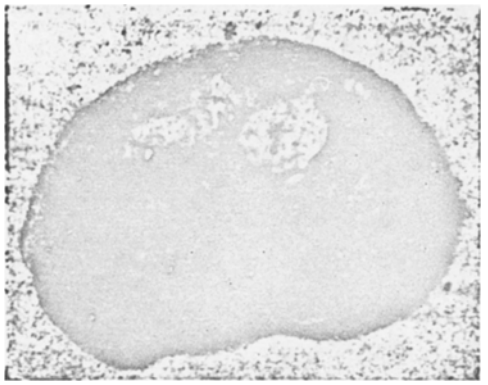

Fig. 1. Foci of dedifferentiation and scarring on the site of former metastases in rabbit No. 117/717 3$^1/_2$ years after treatment with ultrasonic waves. Macropreparation.

Our observations have shown that when the Brown-Pearce tumor regresses spontaneously, the tumor nodule gradually diminishes in size until it is totally gone at the end of 1-2 months following the inoculation. The action of ultrasonic waves leads not only to resorption of the nodule subjected to treatment but also, in many instances, to resorption of untreated metastases. In the experimental rabbits the regression of the treated nodule was usually preceded by some growth of the tumor nodule. The regression process of the swelling in the various animals took from 15 days to 5 months. Naturally, we fixed our attention upon the metastases forming in the eyes, lymph glands, and kidneys as we could observe them visually and with the aid of palpation. In addition, the exact condition of the metastases was defined at autopsy and studied further histologically.

Our observations demonstrated that before the treated tumor begins to regress there is some enlargement of the metastatic nodes. Later, these sharply diminish in size and disintegrate. The disintegrated metastases, as was the case with the primary nodule, subjected to ultrasonic waves either became replaced by scar tissue, became dedifferentiated and encapsulated, or else vanished without leaving any trace. The process of metastatic disintegration lasts a long time and ends only long after the primary nodule has disappeared completely. Thus, in some instances it took 7 months for the metastases in the lymph glands, eyes and kidneys to dissolve.

We present our data in the following concrete observations.

Instance 1. Regimen of treatment: frequency 750 kilocycles, power 34 W/cm^2, exposure 15 seconds repeated five times. The contact was aided with vaseline.

In rabbit No. 780 the tumor was inoculated into the muscle of the right thigh. Eleven days later the tumor nodule was subjected to ultrasonic waves. Within 2$^1/_2$ months the tumor had dissolved. By that time the lymphatic gland under the knee could be palpated as being thickened. Nine months later the rabbit was sacrificed and autopsied, and a scar was found at the site of the primary nodule. The lymphatic gland under the right knee and the right adrenal were walnut sized, thickened and surrounded by a dense capsule which when sectioned had the appearance of a reddish caseated mass. Microscopic section revealed dystrophic tumor tissue. Fields of complete lysis of tumor elements alternated with areas consisting of small rounded cells with wrinkled, dark eccentrically placed nuclei. In the lungs there were also found large disintegrated metastatic nodes, the size of walnuts, and smaller ones no larger than small peas. In these latter, histological studies showed cellular disorganization, vacuolization and pyknosis of the nuclei, karyorrhexis.

Thus, in this rabbit, after the disintegration of the treated primary nodule, resorption of metastases took place in the lungs, adrenals and lymph gland below the knee. The ultrasonic regimen as outlined produced similar regression of metastases in 3 more rabbits: Nos. 559, 749 and 781.

Instance 2. Regimen of treatment: frequency 1500 kilocycles, power 27 W/cm^2, exposure 17 seconds. Ultrasonic waves were conducted through water.

Rabbit No. 117/717 was inoculated intratesticularly with the tumor, the testicle having been placed under the skin of the right thigh. Eight days later, the rabbit was subjected to treatment. On that day the tumor measured 5 x 1 x 1.5 cm. It continued to enlarge for 2 month; after the application of ultrasonic waves. Its dimensions reached 7.5 x 4 x 2 cm. By this time the rabbit had metastases in the right eye and in the kidneys. Starting at 2 months after the treatment, the tumor began to decrease and was fully resorbed after 5 months. The metastasis observed in the right eye became necrotized. After 3 months the disintegrated tumor in the eye began to separate from the eye ball. After 4 months the orbital depression was clear of the necrotic mass and the rabbit began to move the eye-lids freely. The metastases in the kidneys were palpable as hillocks for almost 6 months. Then they began to decrease in size and could not be palpated at 7 months. The rabbit was sacrificed 3$^1/_2$ years after the ultrasonic treatment. At autopsy both kidneys were seen to have dense rounded foci of dedifferentiation of about 5-8 mm diameter. (Fig. 1). Histological examination confirmed the dedifferentiation and scar transformation of the tumor mass (Fig. 2).

Fig. 2. Scar at the site of former metastases in the kidney (same rabbit as in Fig. 1). Section stained with picrofuchsin (enlargement 10 x 10).

Thus, in this instance, following regression of the treated tumor the metastases in the eye resorbed after 4 months and in the kidneys after 7 months.

In rabbits, No. 17 and 10/611, subjected to the same treatment, regression of the primary tumor inoculated intratesticularly was observed, this being followed by resorption of the tumor conglomerates in the seminal canal, measuring 4 x 1.5 cm, which had not been treated.

In subsequent experiments we tripled the intensity of the ultrasonic waves and correspondingly shortened the exposure time. In the treated rabbits we observed complete cessation of the tumor process as described below.

Instance 3. Regimen of treatment: frequency 1500 kilocycles, power 87 W/cm^2, exposure 3 seconds. The ultrasonic waves were conducted through water.

In rabbit No. 708 the tumor was inoculated into the testicle displaced forward under the skin. Seven days following the inoculation, the tumor, measuring 3.5 x 2.5 x 1 cm was subjected to treatment. For the first 10 days following the treatment the tumor continued its growth attaining 5 x 3 x 1.5 cm. Then the tumor nodule began to soften and decrease in size. 1$^1/_2$ months after the procedure the swelling had fully resorbed. 4 months later the rabbit was sacrificed and at autopsy disintegrated petrified metastases were found in the right lymph gland and adrenal.

In rabbit No. 707 from the same experiment the tumor grew at first markedly after the experimental treatment but then began to regress and became encapsulated, remaining about walnut sized. 17 days after the procedure there appeared metastases in the left eye and in the kidneys where they could be felt on palpation as hillocks. 3 months later the kidney metastases could no longer be felt. The rabbit died 5$^1/_2$ months from the day of inoculation as a result of a traumatic paralysis of the posterior extremities. Histological investigation of the treated tumor nodule showed a picture of total necrosis of the cancer tissue and formation of focal dedifferentiation. Both kidneys appeared normal in size. On their surfaces, where previously the metastases could be palpated, there were numerous depressions of varying size with a whitish, convex bottom. Histological examination of these areas uncovered coarse fibrous scar tissue.

Fig. 3. Organization of a liver metastasis in rabbit No. 117 three weeks after ultrasonic treatment. Section stained with picrofuchsin, enlargement 7×8.

Instance 4. In these experiments the intensity of the ultrasonics was 5 times that used in the first experiments, while the decrease in exposure time was 7-fold. System of treatment: frequency 1500 kilocycles; power 150 W cm^2; exposure 1.3 seconds; ultrasonic conduction through water.

In these experiments also, we observed that along with resorption of the treated primary tumor regression of the untreated metastases took place. Thus, in rabbit No. 80 the tumor dissolved $1^1/_2$ months after the procedure. By that time, the right eye was observed to have a large metastasis. 5 months later the eye metastasis disintegrated, the necrotic masses sloughing out. Another rabbit, No. 117, was sacrificed 3 weeks after the ultrasonic treatment and a liver metastasis could be seen organizing (Fig. 3).

Summarizing our experiments, we draw the following conclusions:

1. The action of high-intensity ultrasonic waves leads to disintegration of Brown-Pearce tumor nodules in rabbits and, in many instances, leads to disintegration and resorption of untreated metastases in such places as the eyes, lungs, liver, adrenals, lymph glands and so on.

2. Just as with the treated primary tumor nodules, the disintegrated metastases may be replaced by scar tissue, dedifferentiated and encapsulated or tracelessly resorbed.

This must mean that high-intensity ultrasonic waves not only act directly on the primary tumor but also, apparently, produce such alterations in the animal organism that the entire cancerous growth is checked and regresses. This problem must become the subject of special investigations.

SUMMARY

The action of high-intensity ultrasonic waves leads to disintegration of Brown-Pearce tumors inoculated into rabbits a week or more previously. In addition, the untreated metastases have been shown in many instances to undergo similar regression. Just as with the primary, treated nodule, they become replaced by scar tissue, dedifferentiate and encapsulate or resorb tracelessly.

This must mean that the intense ultrasonic waves act not only on the primary tumor directly, but also, must produce basic alterations in the animal organism as a whole which enable it to check the developing cancer everywhere in the body.

This fundamental problem must become the subject of special investigations.

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