Plasma Antitrypsin Levels during Growth of a Rat Fibrosarcoma

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The rise of antitrypsin concentrations in patients with malignant neoplasms has been reported by us (5) and by several others (1—8). However, no evaluation of the levels at the time of origin or during the growth of the tumor was possible. It seemed desirable, therefore, to ascertain whether antitrypsin values would be useful in determining the stage of tumor development and in what circumstances these values could be misleading. Since it was impossible to obtain human material for this in vivo study, rats were selected as suitable animals for comparison.

EXPERIMENTAL

Fifty-one male rats of the Sprague-Dawbey strain were bled by cardiac puncture and then implanted in the inguinal region with a fibrosarcoma explant. The tumor was originally induced at this hospital with methylcholanthrene and carried through six generations of transplantations. The rats used were fed ad libitum on laboratory chow throughout the study. Together with six control rats which received no implants, the implanted rats were bled 10 days after implantation and at 2-week intervals thereafter for 3 months. One cc. of blood was withdrawn with a syringe containing 2 mg. lithium oxalate. The plasma removed from this blood was used in the determination of antitrypsin according to Wells et al. (6). At each bleeding the inguinal region was palpated, the size of the implant was noted, and the rat was weighed. White blood counts and differential white counts were made.

RESULTS

On the basis of the tumor activity in the individual rat, the data on the animals were arranged in three groups: I. implant did not grow—non-takes; II. implant grew and then disappeared—regressions; III. implant grew into a well-developed tumor—takes. Group III was subdivided into two sections: (a) tumor remained firm and well defined throughout the period of study and (b) tumor showed early degeneration and erosion.

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Of the 51 animals investigated, 20 fell into Group I, 13 into Group II, 10 into III, a, and 8 into III, b. After data on each rat had been assigned to a certain group, the antitrypsin levels and blood pictures were studied statistically. In Figs. 1-4, the trends of antitrypsin content and total white counts and lymphocytes are shown for the various groups. The curves were drawn from mean values in scatter diagrams. Of course, greater changes could be noted with individual animals, but since most previous reports on humans were given as averages, this method of presentation was selected. As can be seen from the curves, the non-takes showed essentially the same picture as the control animals and leveled off at the same period. In Group II a significant increase in antitrypsin values became apparent at 28 days and gradually returned to normal preimplantation levels. Some interesting observations were made concerning Group III, b. Although erosion of the tumor occurred at different stages in individual animals, the respective antitrypsin values consistently decreased to preimplantation levels as soon as necrosis was complete. In three cases the entire tumor was removed at onset of erosion, and the anti-
trypsin concentrations had decreased toward control levels by the time of the next bleeding.

In the four figures the relationship between total white blood count and antitrypsin in tumor preimplantation levels after necrosis and after surgical removal of the tumor.

In several of the animals of Group II, a large, fluid-filled cyst formed at the site of implantation. The serosanguinous fluid was removed by aspiration from the sac and its antitrypsin content measured. The amount of antitrypsin it contained was approximately the same as that of normal human plasma. No white cells were demonstrable.

DISCUSSION

In order to deduce any clinical significance from this study, one must remember that rats have a normal antitrypsin and a normal white count which is twice that of humans (4). The fibrosarcoma used is not comparable to any human neoplasm studied. These results, however, lend support to the findings of previous investigations on human cancer patients at this hospital (5). It can be seen that in cases of rapidly growing tumors, the antitrypsin levels and white blood counts are
elevated. Interesting deductions can be made concerning regressing tumors. In this group, as in that in which the tumor continued to grow, the antitrypsin gradually increased to significant values between 28 and 42 days. It is probable, therefore, that this is the “critical period” in which the fate of the tumor is determined. The tumor then either grows or regresses with corresponding elevation or depression of antitrypsin and white blood count. The fact that concentration of antitrypsin and total white blood count so closely parallel each other is indicative of the role played by white cells as carriers of antitrypsin. Since the lymphocyte content varies inversely with the amount of antitrypsin, it would seem that the polymorphonuclear white cells are selectively involved in antitrypsin activity. This is borne out by the fact that neutrophilia appears in the same clinical conditions in which antitrypsin content increases (9). Further work on this subject is needed for proof, but several authors (7, 8) have intimated the role of white cells in tryptic and antitryptic activity. The results found here are most important in corroborating our previous findings—that the determination of antitrypsin may not serve as a diagnosis, but, together with additional clinical data, may give valuable information about the status of the tumor and the health of the patient. These results show that ground work for other problems of this type can be facilitated by studies on rat tumor growth in vitro.

SUMMARY

1. Antitrypsin levels and white blood counts at various stages in the growth of a rat fibrosarcoma are reported. There is an elevation of both during the period of most rapid growth.

2. Upon regression and after surgical removal of the tumor, the antitrypsin and white blood count decrease.

3. Control animals and those in which the implant does not take give essentially the same results, with no significant increase in either antitrypsin or white blood count.

4. Serosanguinous fluid accumulating in cysts in regressing tumors contains some antitrypsin but no white cells.

REFERENCES


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