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STUDIES ON THE USE OF MUMPS VIRUS FOR TREATMENT OF HUMAN CANCER

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SUMMARY Purified mumps virus (Urabe strain) was given mainly by intravenous injection to a total of 200 patients with cancer. The only adverse clinical reaction was transient mild fever in about half the patients. The beneficial clinical effects were as follows; decrease or disappearance of ascites and edema of the lower limbs at high rates (26/37 and 4/4, respectively), usually within a week after treatment: decrease or stoppage of cancerous bleeding in 30 of 35 patients: decrease or disappearance of pain in most of the patients: and tumor regression in 26 patients with cancer of the breast, rectum, ileocaecum, thyroid gland, uterus, skin, etc. Histologically, the virus-treatment caused shrinkage of nuclei and vacuolization of the cytoplasma of tumor cells, but the degenerative changes of tumor cells were not so great as those after chemotherapy or radiotherapy. Infiltration of lymphocytes, fibrosis and collagenesis occurred around tumor tissues, where necrosis or exfoliation of tumor cells was frequently observed.

INTRODUCTION

It was previously reported that administration of mumps virus had some curative effects on human cancers (Asada, 1974). Since then, the purity and quantity of virus materials have been improved and thus more beneficial effects on human can be observed. The results of a trial on 200 human cases of cancer are presented in this paper.

MATERIALS AND METHODS

1. *Virus*

The Urabe strain of mumps virus (MV, Yamanishi et al., 1970a), isolated in human embryonic kidney (HEK) cells was used as seed virus. Virus material was prepared as follows: Seed virus was inoculated onto HEK cells or established human amnion cells (AV3) at an input multiplicity of about 1 and the cells were incubated at 37 C. After 4 to 5 days, the medium was decanted and the cell sheet was washed repeatedly with phosphate buffered saline (PBS). Fresh medium 199 containing 0.1% human albumin and supplemented with leucomycin (50 μg/ml) and erythromycin (50 μg/ml) was added and incubation was continued for further 2 to 3 days. After the appearance of extensive cytopathic change, the fluid was centrifuged at 2,000 rpm for 20 min at 4 C to remove cell debris and the supernatant was used as virus material, after confirmation that it contained no extraneous microbes.

2. *Patients*

A total of 200 patients with various kinds of cancer were treated with mumps virus (Table 1). Most of the patients had advanced stages of cancer.

TABLE 1. *Number of cancer patients treated with mumps virus*

Cancer	National Osaka Hospital	Higashi-Osaka Central Hospital	Others	Total
Stomach	27	46	27	100
Rectum		14	6	20
Breast		11		11
Colon	1	6	1	8
Bile duct	2	6		8
Liver	5		2	7
Pancreas	3	1	2	6
Lung	1		5	6
Uterus		2	4	6
Ovarium		4	2	6
Oesophagus	1	1	2	4
Skin		3		3
Bladder		1	1	2
Thyroid gland		2		2
Kidney	1		1	2
Tongue			1	1
Pharynx			1	1
Prostata			1	1
Melanoma			1	1
Others	1	3	1	5
Total	42	100	58	200

3. *Virus material and methods of application to cancer patients*

Under the culture conditions used virus material with a virus concentration of 10^{6-7} PFU(plaque forming unit)/0.1 ml with no adventitious protein other than that of human origin could be obtained. Virus materials were stored at -70 C until use. They were thawed in a water bath at 37 C just before use and administered to patients usually intravenously, or by inhalation or sometimes locally. Ten milliliters of virus material was usually used for one intravenous injection. Usually, no chemotherapy nor radiotherapy was given to the patients during treatment with MV.

4. *Reisolation of mumps virus from the treated patients*

Throat swabs were collected daily from the patients after MV treatment. Swabs were soaked in a small amount of Eagle MEM (minimum essential medium), the fluid was centrifuged at 3,000 rpm for 20 min, and the supernatant was inoculated onto HEK cells. After incubation for 1 week at 37 C, the fluid was inoculated onto fresh HEK cells. Cultures were incubated for another week and then the fluid was decanted and MV was detected by the hemadsorption test with chicken red cells.

5. *Virus titration*

The infectivity of virus was titrated in HEK cells by the hemadsorption method with chicken red cells. The infectivity titer was read 7 days after infection (Yamanishi et al., 1970a).

6. *Assay of neutralizing (NT) antibody*

Neutralizing antibody was assayed in microplates (Linbro Co., New Haven, Conn., USA) sterilized by UV-irradiation for 15 min. A volume of 0.025 ml of diluent (PBS containing 0.2% gelatin and 200 μg/ml kanamycin) was dropped into each well with a 0.025 ml dropper (Microtiter, Cook Engineering Co., Alexandria, Va., U.S.A.). Serum specimens

were serially diluted in the well with 0.025 ml diluters which had been sterilized in a flame before use. Then 0.025 ml of antigen containing about 100 $TCID_{50}$ of mumps virus (Miyake strain) was dropped into each well and the serum-virus mixture was shaken well. The mixture was incubated for 1 hr at 37 C, and then kept overnight at 4 C. On the following day, 0.1 ml of LLC-MK_2 cells (about $2\times10^{4.0}$ cells/0.1 ml) was added to the serum-virus mixture and the microplate was incubated at 37 C in a CO_2 incubator. The culture fluid was decanted on the 6th or 7th day after inoculation, 0.05 ml of a 0.5% suspension of chicken red cells was put into each well and the microplates were kept at room temperature for 30 min. The NT antibody titer was expressed as the highest serum dilution at which hemadsorption was inhibited.

7. *Inhibition of lymphocyte transformation by serum of cancer patients*

The serum-inhibitory factor for in vitro lymphocyte transformation in cancer patients was measured by the method of Sample et al. (1971). O-type blood cells were collected, and washed 3 times with RPMI medium by centrifugation at 2,000 rpm for 30 min, and resuspended in RPMI medium to give a 10% blood cell suspension. AB-type serum collected from healthy persons was used after heat inactivation as control serum.

Sera taken from the cancer patients were heat-inactivated and a 0.1 ml volume was mixed with 1 ml of O-type blood cell suspension prepared as above and 0.025 ml of PHA (phytohemagglutinin, Difco, 13 μg/ml) and incubated at 37 C. After 48 hr, ^{3}H-thymidine (0.025 ml, 1.25 μCi) was added and incubation was continued for 24 hr to allow incorporation of ^{3}H-thymidine into DNA synthesized in the leucocytes. Then the cells were collected and washed on a glass fiber filter, and their radioactivity was counted in a scintillation counter. The ratio of the radioactivity with serum of the cancer patients to that with control serum was calculated. A ratio value of 1 indicated that no inhibitory factor was present, whereas a value of less than 1 indicated the presence of an inhibitory factor in the serum of the cancer patients.

RESULTS

1. *Virological and immunological examination*

1) Growth of MV in cells of human origin and tissues from cancer patients

MV replicated well in established human cells (FL, HeLa and KB cells), reaching a titer of more than $10^{5.0}$ $TCID_{50}$/0.1 ml at 5 to 7 days after inoculation and causing cytopathic changes.

Virus growth was examined in tissues from a patient with gastric cancer. Organ cultures of the tumor (basal, and mucous membranes), non-tumor tissue of the stomach (mucous membrane) and a lymphnode were made in 60 mm plastic dishes and 0.1 ml of MV (10^6 PFU/0.1 ml) was inoculated into each dish with 7 ml of 199 medium. Cultures were incubated at 37 C and fluid was harvested and titrated every 2 days.

As shown in Table 2, slight growth of MV was detected only in the mucous membrane of the tumor.

TABLE 2. *Growth of mumps virus in organ culture of tissue from stomach cancer (52-year-old man)*

Site	Virus titer (log/0.1 ml) (days after inoculation) 2	4	6	8
Tumor (Basal)	0.5	0	0	0
Tumor (Mucous membrane)	1.0	1.5	1.5	1.5
Non-tumor (Mucous membrane)	0	0	0	0
Lymphnode	0	0	0	0
Control (Virus+199 medium)	1.5	0	0	0

2) Recovery of mumps virus from patients receiving MV treatment (MVT)

Attempts were made to recover the mumps virus from 3 patients inoculated intravenously with MV. No mumps virus could be recovered from them for at least 9 days after the inoculation. Furthermore, no contact infection was observed from recipients of MV to susceptible subjects in homes or hospitals.

3) Neutralizing (NT) antibody response

Most patients (27 of 29 examined) were

found to have NT antibody for mumps virus before treatment. The antibody responses in 11 patients are shown in Fig 1. In 9 patients who received MVT by the intravenous route, a rise of NT antibody was detected 4 to 5 days after treatment, suggesting that secondary infection occurred in them. There was no definite correlation between the degree of the antibody response and the improvement of treated patients. No antibody response was observed in 2 patients who received MV orally.

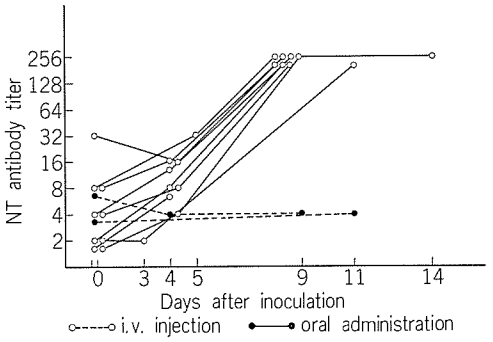
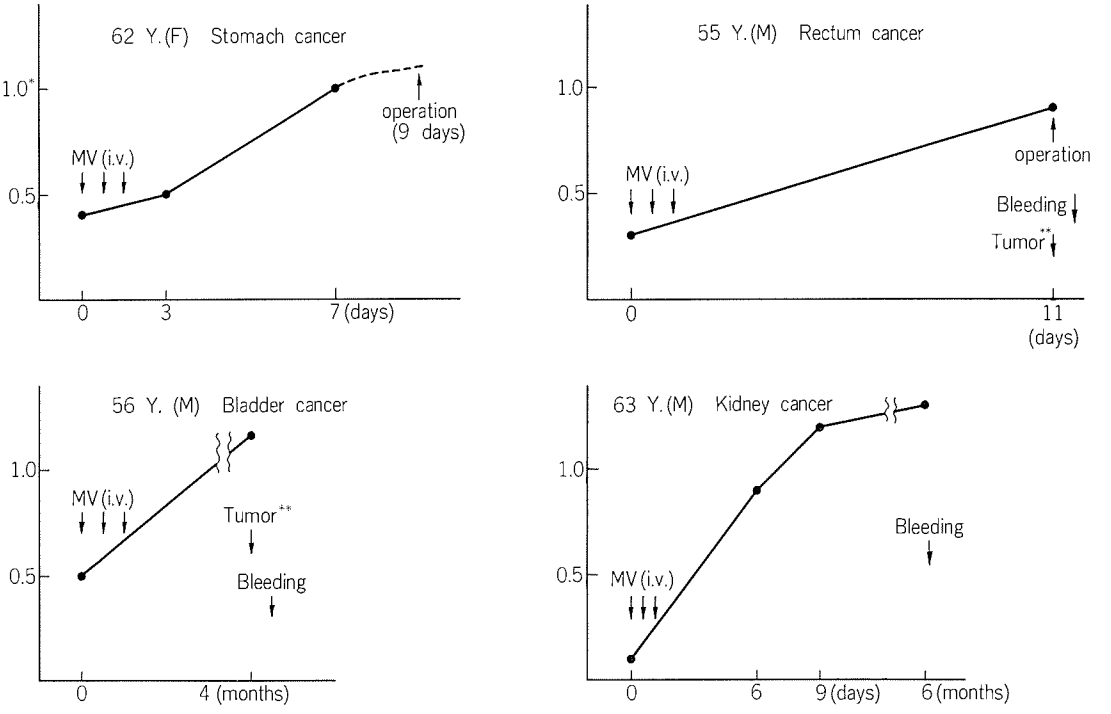


FIGURE 1. Neutralizing(NT) antibody response in cancer patients treated with mumps virus.

4) Lymphocyte transformation test

Inhibition of in vitro lymphocyte transformation by sera of some of the patients was examined. An apparent decrease of the inhibitory factor was observed several days after MVT in cases of cancer that were not in an advanced stage and also in cases in which subjective clinical symptoms were improved over a long period. Examples of these cases are presented in Fig 2. No clearcut results were obtained in cases in the terminal stage of cancer.



* The ratio of radiocounting of ^{3}H-thymidine incorporated into DNA of PHA-stimulated lymphocytes incubated with serum of cancer patient to that of control healthy person.

** Regress or decrease.

FIGURE 2. Plasma inhibitory effect of cancer patients on PHA-stimulated lymphocytes.

TABLE 3. *Clinical findings after treatment with mumps virus*

	National Osaka Hospital	Higashi-Osaka Central Hospital	Others	Total
Feverish reaction (temporary)	17 (42)[a]	57 (100)	30 (58)	104 (200)
Regression of tumor	1	13	12	26
Decrease or disappearance of ascites	10 (12)	10 (17)	6 (8)	26 (37)
Decrease or suspension of bleeding		12 (12)	18 (23)	30 (35)
Disappearance of edema of lower limbs		4 (4)		4 (4)
Suspension of hemosputum or cough			2	2
Alleviation or disappearance of pain	3	16	11	30

[a] Figures in parentheses indicate numbers of treated patients (the parameter).

2. *Clinical and pathological findings in patients receiving MVT*

The principal clinical findings in cancer patients after MVT are shown in Table 3.

1) Adverse clinical reaction

The only adverse clinical reaction observed was transient fever. About half the treated patients developed transient fever, usually half an hour to 2 hours after intravenous injection of MV, and a temperature of about 38 C, or rarely 40 C, lasted for several hours, but seldom for more than 24 hr. The fever reaction usually occurred after the first administration of MV and became negligible after repeated injections. No leucopenia, nor other changes in laboratory findings was observed after MV treatment.

2) Effect on cancerous pain

Alleviation of cancerous pain was noticed in 30 cases, in most of which the effect developed several days after MV treatment.

Case 1. 50-year-old woman

On July 22, 1975 the patient received a surgical operation for a suspected right ovarial tumor, but she was found to have an advanced tumor in the ileocaecal region with metastasis. This tumor was diagnosed histologically as an adenocarcinoma, but its removal was impossible. She complained of severe pain of the ileocaecal region. MV was given intravenously and her pain disappeared for 3 days from the following day. Accordingly she asked to have further MVT and was given injections once a week. After every treatment the pain disappeared for 2 to 3 days. Intravenous injection of MV was repeated 18 times and no adverse reaction was noticed.

3) Effect on cancerous bleeding

Suspension of cancerous bleeding was noticed in 30 of 35 cases after MVT, and 12 cases seen at Higashi-Osaka Central Hospital are shown in Table 4. In most cases, bleeding stopped within 3 days after MVT, and in 4 cases it did not start again for more than 100 days.

Case 2. 49-year-old woman (No. 3 in Table 4)

In December 1974, the patient was diagnosed clinically as having advanced ovarial cancer and received an operation. She visited the out-patient clinic on Jan. 20, 1975 complaining of heavy ascites and uterous bleeding, and received MVT for 3 consecutive days. A transient fever of 37 C was noticed, but the ascites completely disappeared within 2 weeks and uterine bleeding markedly diminished. She recovered her appetite and no increase of ascites was noticed during the following 6 months.

4) Effect on edema of the lower limbs

Disappearance of edema of the lower limbs due to tumor around the inguinal region was observed shortly after intravenous injection of

TABLE 4. *Suspension of cancerous bleeding after treatment with mumps virus*

Case No.	Age & Sex	Cancer	Days until suspension of bleeding after MVT	Days of suspension of bleeding	Nature of bleeding
1	65 M	Stomach	1	11	Repeated extensive bleeding
2	61 F	Ovarium	3	30	Uterine bleeding
3	49 F	„	18	270	Uterine bleeding
4	32 F	Ileocaecum	1	40	Much melena
5	77 M	Rectum	1	10	„
6	73 F	Breast	2	20	Bleeding from the surface
7	74 M	Rectum	1	150	Much melena
8	60 M	„	1	120	„
9	72 M	Bladder	1	80	Hematuria
10	82 M	„	2	80	„
11	66 F	Skin	2	100	Bleeding from the skin
12	35 M	Rectum	1	12	Much melena

TABLE 5. *Disappearance of edema of lower limbs after treatment with mumps virus*

Case No.	Age & Sex	Cancer	Days until beginning of decrease of edema (days)	Description
1	62 F	Stomach	3	Metastasis in inguinal lymphnode
2	50 M	Hodgkin's disease	7	Enlargement of inguinal lymphnode
3	53 F	Uterus	3	Metastasis in pelvis and obstruction of vein
4	44 F	Uterus	3	Metastasis in inguinal lymphnode

MV in 4 cases (Table 5).

Case 3. 53-year-old woman (No. 3 in Table 5)

The patient noticed edema of the left leg at the beginning of 1975. Her leg became painful in November of the same year and she was admitted to the hospital in February 1976. The circumferences of the right and left legs were 42 cm and 54.5 cm, respectively, and a tumor with the size of a fist was palpable in the left inguinal region. On surgery on Feb. 25, the tumor was found to have originated from the uterus, expanding into the retroperitoneal region. The left ureter and the vena ilica were completely blocked and removal of the tumor was impossible. On the 7th day after the operation, MVT was given for 7 consecutive days. No chemotherapy or diuretic was given, and her leg was not kept in a raised

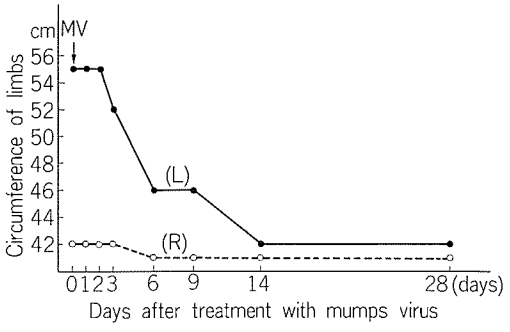


FIGURE 3. Change in circumferences of lower limbs of cancer patients after treatment with mumps virus.

FIGURE 4. Lower limbs of a case of uterus cancer (Case 3 in Table 5) before MVT.

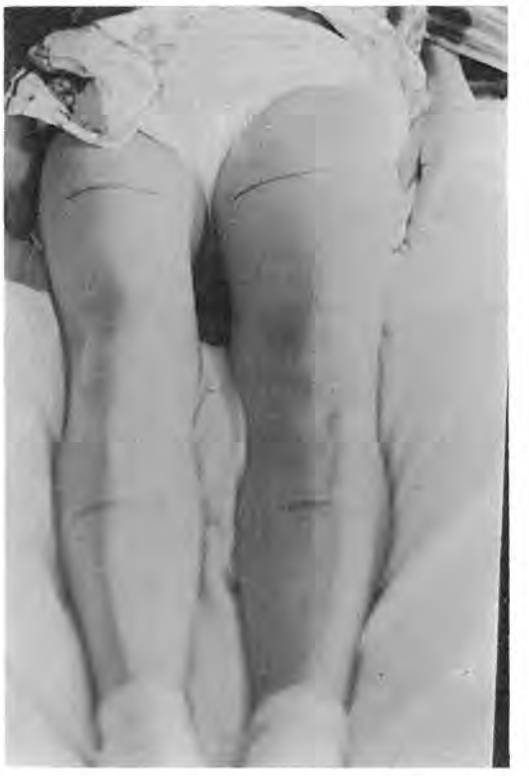


FIGURE 5. Lower limbs of the same case as in Fig. 4. on day 14 after MVT

position. The edema began to decrease 3 days after MVT and almost completely disappeared within 2 weeks (Fig. 3, 4, 5). No re-development of edema was noticed within 3 months.

5) Effect on cancerous ascites

Decrease or disappearance of ascites was noticed in 26 of 37 patients after MVT. The effects were observed in cases where a diuretic was no longer effective, and their duration varied, being several months in 2 cases.

6) Tumor regression

Tumor regression was noticed in 26 cases after MVT, usually beginning within 7 days after treatment. Table 6 shows data on the 13 cases treated at Higashi-Osaka Central Hospital. In addition, tumor regression was also observed in 5 cases of gastic cancer, 2 cases of uterus cancer, and 1 case each of lung cancer, colon cancer, breast cancer, bladder cancer, melanoma and kidney cancer in other hospitals.

Case 4. 73-year-old woman (No. 3 in Table 6)

The patient visited the out-patient clinic on Nov. 25, 1975, with a breast tumor that apparently invaded the skin and severe bleeding. The tumor was diagnosed as an adenocarcinoma by biopsy. MVT was given from Dec. 1 for 15 consecutive days. The tumor began to regress on the 4th day of MVT with disappearance of bleeding of the skin in the tumor region. On the 16th day, the tumor had regressed to about one third of its original volume with disappearance of erosion (Fig. 6, 7). Subsequently surgical operation was carried out. On pathological examination, degenera-

TABLE 6. *Cases of tumor regression after treatment with mumps virus*

Case No.	Age & Sex	Cancer	Method of administration of MV	Change in size of tumor (diameter, cm)	Days until tumor regression	Tuberculin reaction before MVT (mm)
1	42 F	Breast	i.v. 3 days consecutively	10×10 → 7×7	7	20×15
2	71 F	„	„	3×2 → 0	3	2×2
3	73 F	„	i.v. 15 days consecutively	13×9×7 → 10×8×5	4	10×10
4	35 F	„	i.v. 3 days consecutively	4×4 → 0	4	12×12
5	72 F	„	„	4 → 3	3	3×3
6	77 M	Rectum	„	5×4×2 → 3×2×0.5	7	35×20
7	70 F	„	„	4×3×1.5 → 3×2×0.5	7	8×10
8	68 F	Thyroid	„	5 → 3	7	
9	50 M	Hodgkin's disease	„	3×2× → 0	7	0×0
10	60 F	Ileocaecal's tumor	intraarterial injection	6 → 3	5	0×0
11	88 F	Colon	i.v. 3 days consecutively	13 → 10	3	22×28
12	44 F	Uterus	i.v. 40 days consecutively	11×6 → 4×3	7	
13	66 F	Skin	i.v. 70 days consecutively	7×11 → 4×9	3	5×5

FIGURE 6. Breast cancer (Case 3 in Table 6) before MVT.

FIGURE 7. Breast cancer of the same case as in Fig. 6. on day 14 after MVT (i.v. 4 days consecutively).

tion of cancer cells, forming clusters of shadowy cells, was prominent in the area of hemorrhagic erosion.

3. *MVT for early gastric cancer*

Five patients with early gastric cancer confirmed by examination with a gastric fiberscope or by biopsy were treated with MV before surgical operation (Table 7), and the tissues removed were examined histologically. On gross examination, disappearance of excavated ulcers suggesting regression of the tumor was noticed in all cases (Fig. 10, 11). On microscopic examination, degeneration of nuclei of cancer cells was noticed and infiltration of lymphocytes was prominent in the submucosal area (Fig. 8, 9, 12, 13).

4. *MVT for early pulmonary cancer*

A patient (66-year-old woman) complaining

TABLE 7. *Treatment of patients with the early stage of gastric cancer by mumps virus*

Case No.	Age & Sex	Method of administration	Days until surgical operation	Pathological findings	
				Before treatment	After treatment
1	53 M	i.v. once	18	Tubular adenocarcinoma	Tubular adenocarcinoma
				Superficially depressed and excavated ulcer	Disappearance of excavated ulcer (III)
				(IIc+III, gastroenteroscopy)	Infiltration of lymphocytes in submucosal area
2	62 M	i.v. 14 days consecutively	15	Poorly differentiated adeno-carcinoma	Disappearance of carcinoma cells and ulcer (IIc+III)
				(IIc+III, gastroenteroscopy)	
3	64 M	Selective arterial injection	14	Tubular adenocarcinoma	Tubular adenocarcinoma
				(IIc+III, gastroenteroscopy)	Disappearance of excavated ulcer (III)
					Nuclei of cancer cells appeared lytic
					Infiltration of lymphocytes in submucosal area
4	58 M	i.v. 3 days consecutively	45	Tubular adenocarcinoma	Tubular adenocarcinoma
				(IIc+III, gastroenteroscopy)	Disappearance of excavated ulcer (III)
5	63 F	i.v. 20 days consecutively	20	Carcinoma simplex	Carcinoma simplex
				(IIc+III, gastroenteroscopy)	Disappearance of excavated ulcer (III)
					Abundant signet ring cells
					Infiltration of lymphocytes in stroma, and slight fibrosis

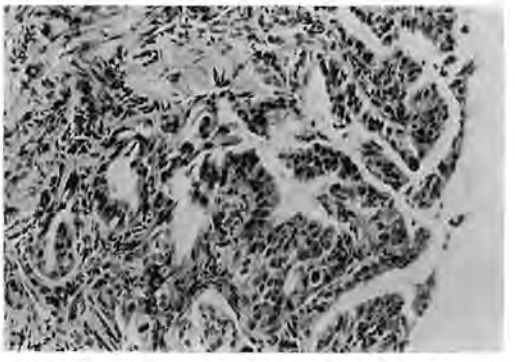


FIGURE 8. Biopsy of early gastric cancer (Case 3 in Table 7) before MVT. Tubular adenocarcinoma.

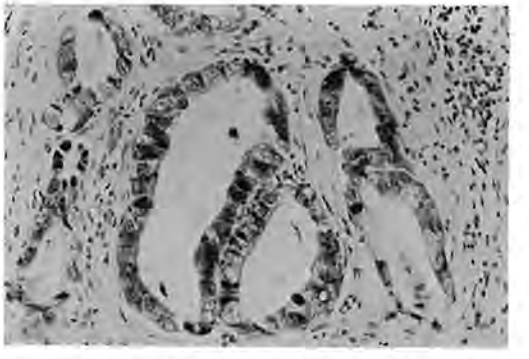


FIGURE 9. Section of resected stomach of the same case as in Fig. 8. on day 14 after MVT. Hydrous degenerative change of the cytoplasma, pycnosis of cancer cells and infiltration of lymphocytes in the stroma are observed.

of a cough and hemosputum was diagnosed as a case of pulmonary cancer by X-ray examination and Papanicolaou staining in Dec. 1974.

She refused to receive a surgical operation or radiotherapy. MVT was given on Dec. 25 to 27 by the intravenous route and inhalation, and then several times by inhalation alone. A few days after the first treatment, the hemosputum completely disappeared and the cough was also alleviated. In Jan. 1975, regression of the tumor was noticed by X-ray examination, and objective clinical symptoms became negligible. No progress of the tumor was noticed in X-ray photos taken in April, June and September of the same year. In July, MV was given again intravenously and by inhalation. The patient is still alive and looks healthy 2 and a half years after MVT.

FIGURE 10. Gastroenteroscopy of a case of early gastric cancer (Case 5 in Table 7) before MVT. An excavated ulcer and its protuberant periphery are seen.

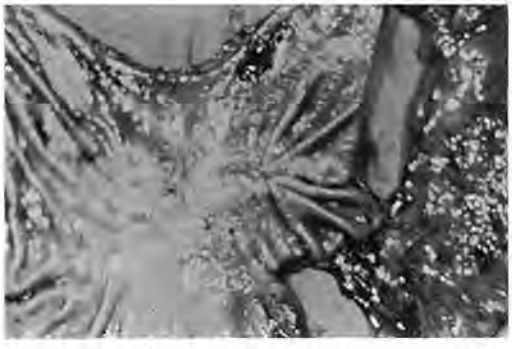


FIGURE 11. Resected stomach of the same case as in Fig. 10. on day 20 after MVT. The excavated ulcer has disappeared and only the concentrated figure of mucosa is observed.

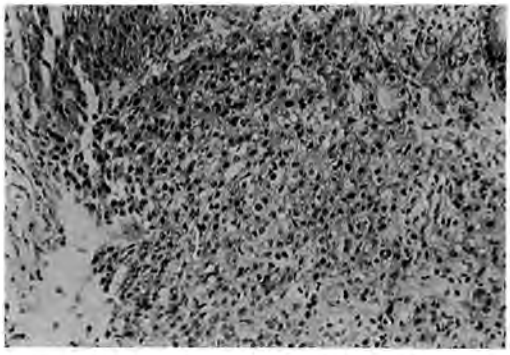


FIGURE 12. Biopsy of early gastric cancer of the same case as in Fig. 10. before MVT. Carcinoma simplex of the mucous membrane.

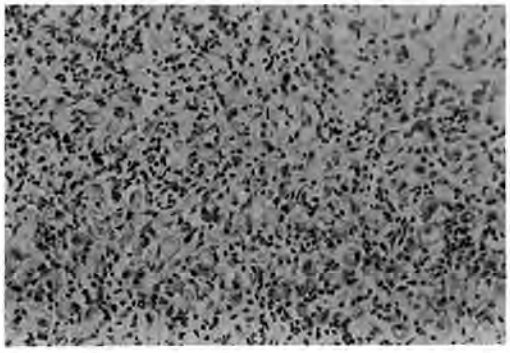


FIGURE 13. Section of the resected stomach of the same case as in Fig. 10. on day 20 after MVT. Signet ring cells showing degenerative changes are abundant and infiltration of lymphocytes is observed.

5. *Pathological findings at autopsy*

On autopsy of cancer patients that received MVT, the following pathological findings were noticed. Degenerative changes of cancer cells were generally not so marked as after radiotherapy or chemotherapy, and no specific histological changes were observed. But shrinkage of nuclei, vacuolization, necrosis and a " hole-like " change, that is degeneration and exfoliation of cancer cells surrounded by stromal tissues were observed. Infiltration of lymphocytes, fibrosis and collagenesis were prominent around cancerous tissues (Fig. 14, 15, 16, 17).

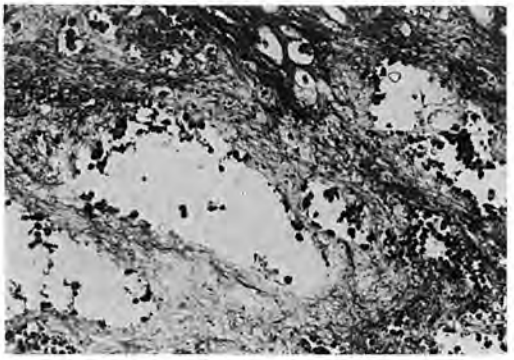


FIGURE 14. Autopsied case of bile duct cancer, 3.5 months after MVT (i.v. 3 days consecutively). Necrosis and exfoliation of cancer cells, and fibrosis with hyaline degenerative change are seen.

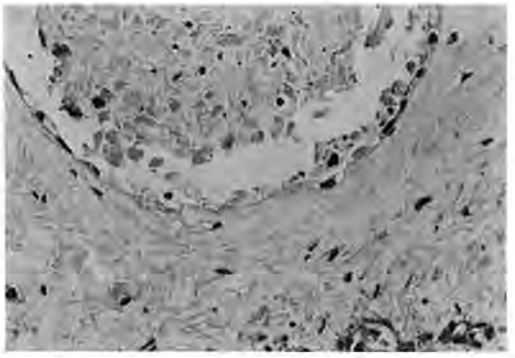


FIGURE 15. Another field of the same tumor as in Fig. 14. Detached cancer cells are observed in the cavity and fibrosis is in progress around the tumor.

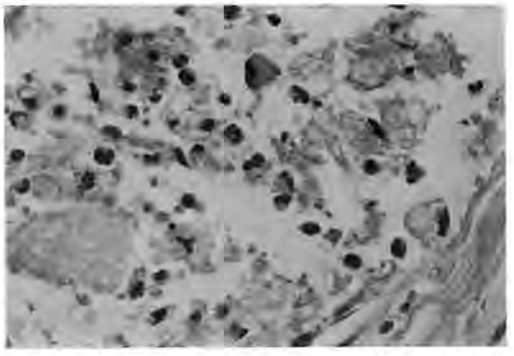


FIGURE 16. Degenerative change of metastatic cancer cells in the lymphnode from stomach cancer, 47 days after MVT (i.v. 3 days consecutively). Shrinkage, degeneration of nuclei and vacuolization of the cytoplasm are seen.

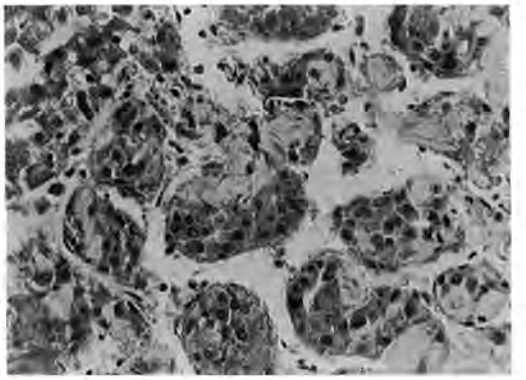


FIGURE 17. Autopsied case of liver cancer, 43 days after MVT (i.v. 3 days consecutively). Degenerative change, necrosis of cancer cells and fibrosis are observed.

DISCUSSION

The oncolytic effects of various viruses on human cancer have been investigated by several workers. Egypt 101 virus was given by the intramuscular or intravenous route to 34 patients with terminal cancer and 5 of them showed tumor regression 2 weeks after the treatment but died in 5 weeks (Southam and Moore, 1952). In addition, West Nile virus, Egypt 101, dengue, mumps, vaccinia, and Newcastle disease virus were also given to patients with cancer, but no apparent morphological changes of the cancer tissues were observed (Newman and Southam, 1954). In 1956, Smith et al. injected adenovirus locally into a patient with uterus cancer and observed suspension of vaginal hemorrhage 4 to 5 days after treatment. Nishioka and his colleagues (Nishioka et al., 1957, Miyazawa et al., 1959) reported that when a kind of influenze virus (ED virus) was given to 50 patients with terminal cancer by intravenous injection, clinical symptoms improved in 11 cases: on histological examination, hypochromatin and degenerative changes of cancer cells were observed in some of these patients. However, a fever reaction, loss of appetite, nausea, vomiting, headache and symptoms of a common cold usually developed and further studies were

discontinued.

In initial studies on MVT, the virus dose was very low and the MV was usually given locally or orally (Asada, 1974). Subsequently the purity and quantity of the virus preparation were improved enabling us to inject a large quantity of virus intravenously. Thus the effect of MV on cancer patients became greater.

The salient features of MVT were rapid disappearance of cancerous pain and edema, including ascites, suspension of cancerous bleeding and improvement of appetite. Slight regression of tumors was occasionally observed. There were no adverse clinical reactions or disturbance of laboratory findings except for transient fever, which was observed after the first few intravenous injections of MV.

On pathological examination, vacuolar degeneration, pycnotic nuclei, swelling of the cytoplasma and karyolysis of cancer cells were observed, but these changes were not so great as after chemotherapy or radiotherapy. These results, together with the finding that there was little growth of MV in tumor tissues in vitro, suggest that a direct oncolytic action may not be the only effect of MVT. MV may have an indirect effect through interferon or hormone production and this possibility requires further examination.

Besides these factors which may work rapidly on cancer patients, long-lasting factors working to suppress tumor growth may be considered. Stimulation of the nonspecific immune capacity of cancer patients by MV infection may reasonably be considered. In addition, Boone et al. (1971) and Kobayashi's group (Hosokawa et al., 1970, Shirai et al., 1971) demonstrated that the immunogenicity of tumor specific antigen was enhanced by infection with influenza virus or Friend leukemia virus. It is conceivable that the same phenomenon may occur with MVT.

On histological examination, infiltration of lymphocytes, fibrosis and collagenesis around tumor cells were observed. Confinement of tumor cells by these tissues would also favor suppression of tumor growth.

Our studies on MVT, especially those on intravenous injection of a large amount of MV, started only a few years ago, and thus we still have no results on the survival of treated patients, which appears the most important factor in evaluation of the effect of chemotherapy or immunotherapy. The appropriate dose of MV, and the time when MV is most effective are unknown, either. Studies on these problems are now under way.

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