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MULTIPLE (FOUR) PRIMARY MALIGNANCIES IN ONE PATIENT

(multiple primary malignancies)

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We experienced a patient with a very rare multiple, primary malignancy. A 56-year old Japanese woman had four cancers on the epipharynx (T2N1M0, poorly differentiated squamous cell carcinoma), left maxillary sinus (T3N0M0, moderate differentiated squamous cell carcinoma) and nasal septum (T1N0M0, poorly differentiated squamous cell carcinoma), separately, seven years after radical surgery for left mammary cancer (papillo-tubular carcinoma).

The incidence of multiple primary cancer is on the increase in Japan as the average life span has been extended and there is an enhancemant in the survival rate of cancer patients. Reports of double cancer are relatively numerous, however, documentation of triple and quadruple cancer is rare.

We now report a case of quadruple cancer involving the breast, epipharynx, maxillary sinus and nasal septum.

CASE REPORT

In July, 1973 a 56-year old woman underwent left radical mastectomy and radiation therapy for cancer, at an another hospital. Histologically, a papillo-tubular carcinoma was diagnosed (Fig.1). She resumed normal activities and in March, 1980 she complained of pain when swallowing, tinnitus and headache. A thumb head sized mass was palpated on the left upper

neck. In August, an exploratory excision of the left cervical tumor proved to be metastatic squamous cell carcinoma. On September 30 she was admitted to our clinic for detection and treatment of the primary lesion.

The family history, revealed no hereditary disposition related to a malignant tumor.

Clinical Findings

Neurological examination was normal. Serology, urinalysis and serum biochemical examinations were all within normal limits. Chest X-ray films showed that the mediastinum had shifted to the left and there were fibrotic changes in the left upper lung field. These findings were considered to be related the radiotherapy for treatment of the breast cancer. EBV(Epstein-Barr virus) antibody titer against viral capsid antigen (VCA) was increased 640-fold.

By posterior rhinoscopy, a hemorrhagic tumor mass was observed from the roof of the nasopharynx to left of Rosenmuller's recess. There was a scar of an exploratory excision on the left upper neck, but tumor mass and induration were nil. The left tympanic membrane was slightly retracted. Pathologic findings in the nasal cavity, paranasal sinuses, mesopharynx, hypopharynx, and larynx were nil. A histopathological diagnosis of poorly differentiated squamous cell carcinoma was made following biopsy of the mass in the epipharynx (Fig.2).

Axial CT scan showed a mass lesion from the left wall of the nasopharynx to the depth and which extended to the ipsilateral eustachian tube, medial pterygoid muscle and near the internal jugular vein (Fig.3).

Clinical Course

The epipharynx and bilateral neck each were given 6000R of irradiation with supervoltage (10MV) X-ray. The palatal observation window and left upper neck dissection were performed the second week after completion of irradiation. Tumor tissue in the epipharynx had almost disappeared, but a biopsy of the previous tumor region showed viable cells (IIA according to the Shimozato's pathological classification (1)). Curettage was done, OK-432 (Picibanil 50KE) was injected locally and oxycel cotton

impregnated with ADM (Adriacin 10mg) was patched over the surgical wound. This patching of Adriacin was carried out daily for 10 days. The clinical course was good and she was discharged on February 7, 1981.

At the end of February, 1981 she complained of left nasal obstruction and nasal discharge. Tumor mass was not evident by anterior rhinoscopy. Radiologic views showed an obscure contour of the lateral wall of left maxillary sinus. A yellowish purulent material was observed on the right and a sanguinous purulency was seen on the left, by maxillary irrigation. Contrast radiography of the maxillary sinus showed defects on the left (Fig.4). From that time she complained of dull pain on the left cheek and bloody nasal discharge on the left, but there were no ophthalmic symptoms. A hemorrhagic mass was observed almost in the center of the nasal septum on the left aspect (Fig.5).

Suspecting maxillary and septal cancer, she was re-admitted on April 11, 1981. A biopsy of the tumor mass of nasal septum showed poorly differentiated squamous cell carcinoma (Fig.6). On April 20, 1981, radical surgery for a double cancer was performed. There was a small bone defect on the anterior wall of the left maxillary sinus and a tumor mass in the sinus. Infiltration to the soft tissue of the cheek was nil. A small bone defect was found on the posterior aspect of the zygomatic arch, but backward infiltration was not observed in this region. The tumor was removed by sharp resection since it broke the orbital floor and slightly adhered to the orbital fat (Fig.7). The ethmoid sinus was clear. Subsequently, the medial wall of the maxillary sinus was removed and the central part of the nasal septum was extensively resected. Histopathological diagnosis of the maxillary tumor was, moderate differentiated squamous cell carcinoma (Fig.8).

Hemorrhagic granulation was observed in the ethmoid region about three months after the surgery. A biopsy showed moderate differentiated squamous cell carcinoma. On July 29, 1981, a Hoshino-Killian's incision was made to remove the residual tumor. She was progressing favourably after the surgery until a white coating became evident on the anterior region on the left aspect of the nasal septum. A biopsy revealed recurrence of the septal tumor. On February 24, 1982, the recurrent tumor was removed and on June 12, 1982, she was discharged.

At this writing there has been no evidence of recurrence and

metastasis.

DISCUSSION

In 1932, Warren and Gates (2) defined multiple cancer as:
1) Each of the tumors must present a definite picture of malignancy.
2) Each must be distinct.
3) The probability of one being a metastasis of the other must be excluded.

However, in the head and neck area, unlike other areas, the organs are adjacent and squamous cell carcinoma is often present. When each of cancers presents as squamous cell carcinoma, there is usually no positive evidence that one is not a recurrence or a metastasis of the other. These multiple cancers cannot as yet be differentiated from multicentric cancer. As a criteria for diagnosis of multiple primary cancer, some authors regard the cases as multiple primary cancers where one cancer is not continuous with another and each requires treatment at its own site (3). In our patient also, the second, third and fourth cancers, that is, cancers of the epipharynx, maxillary sinus and nasal septum, and which developed subsequent to breast cancer were in close proximity, but one tumor was not continuous with another macroscopically and each required treatment at its own site. Thus, we classified this as a case of quadruple cancer.

The lymph flows backwards from the epipharynx to the maxillary sinus and nasal septum. There is apparently no documentation of a direct lymph route between the maxillary sinus and nasal septum (4). Thus, the possibility of metastasis of epipharyngeal cancer to the maxillary sinus and nasal septum of from the maxillary sinus to the nasal septum is all but nil. Inuyama et al. maintained that diagnosis of multiple primary cancer can be made, regardless of the duration of each cancer, if the possibility of one cancer metastasizing of the other is low (5). In this sense, the present case may be regarded as one of multiple primary cancer.

Multiple primary cancer may be divided into synchronous and metachronous cancer, according to the interval between the occurrence of the first and second tumor. There is no established criterion to distinguish between the two. Generally, multiple primary cancer with an interval of less than one year is referred

to as synchronous and occurrence with an interval of over one year as metachronous (6,7). According to this criterion, the present case is metachronous. The incidence of multiple primary malignancy in Japan seems to be slightly lower than that in Europe and America, at least at the present. (8-15).

Sasaki et al. (16) analyzed multiple primary malignancies mentioned in the Japana Centra Revuo Medicina that was published from January, 1966 to December, 1970 and reported that there were double cancers in 178, triple cancers in 11, and quadruple cancers in 2. Multiple primary malignancies of quadruple or more as in the present case are very rare (17-20).

Kirikae et al. (21) scrutinized various papers looking for mechanisms by which multiple primary malignancy is produced and stated that the opinions given in these papers could be roughly divided into (a) those that attach importance to hereditary factors, (b) those showing that the first tumor exerts an influence on development of the second tumor and (c) those that maintain that multiple development of cancer is a mere accidental phenomenon. Papers coming under (a) are based on the theory attaching importance to predispositions and conditions related to the physical constitution of the patients. A family history of malignant tumor was nil in our patient. As to the mechanism under (b), however, a complex mechanism including endocrinological abnormality might possibly be involved when one of the multiple primary cancers is found in such related organs, as in our patient (13,21). Inuyama et al. (6) suggested the possible relation of a cancer virus to multiple primary malignancy. In the present case also, it is of interest that EBV-infected antibody titer against VCA in the sera increased up to 640 times during examination of the epipharyngeal cancer, the second cancer to occur. As to the age at the onset of multiple primary malignancy, a decline in the immunological surveillance of the host is presumed to play an important role in the development of multiple primary malignancy. It is also possible that a carcinostatica used in the treatment of first cancer exerted an influence on the immunological surveillance to become one of the factors that led to development of the second cancer (6,7).

As the prognosis of cancer patients improves with the progress of diagnosis and treatment, the number of patients with multiple primary malignancy may possibly increase. Particularly for individuals with a past history of cancer of the stomach,

intestine, lung, esophagus, uterus and breast and in whom multiple primary malignancies may develop, a close follow-up is recommended(22).

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LEGENDS

Fig.1. Papillo-tubular carcinoma of the left breast. HE.X100.

Fig.2. The mass in the epipharynx was composed of polygonal epithelial cells accompanied by aggregation of lymphocytes and showed poorly differentiated squamous cell carcinoma (so-called lymphoepithelioma). HE.X100.

Fig.3. Axial CT scan showed a mass lesion from the left wall of the nasopharynx to the depth.

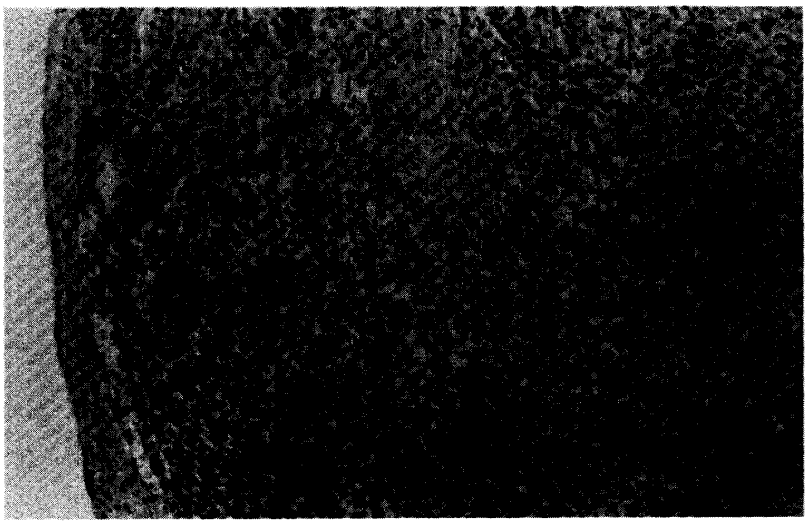
Fig.4. Contrast radiography of the maxillary sinus showed defects on the left side.

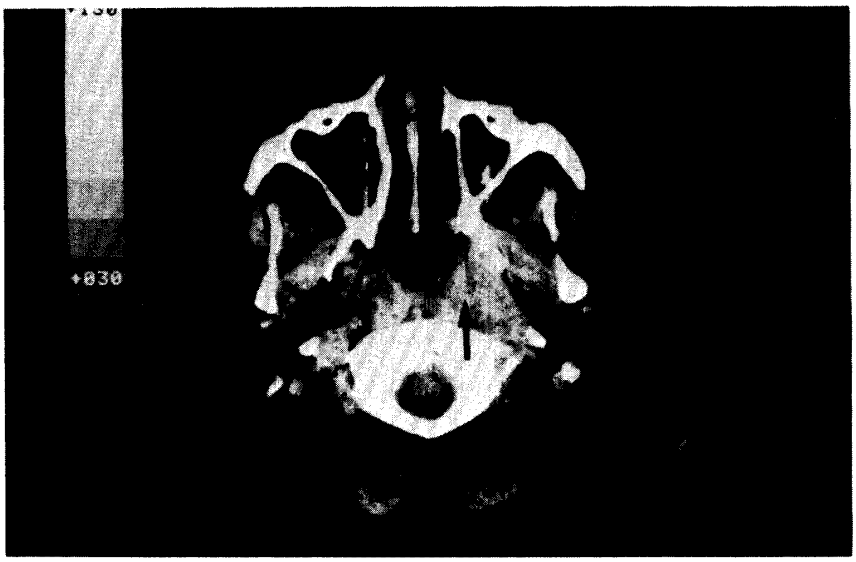
Fig.5. The hemorrhagic mass was located almost in the center of the nasal septum, on the left aspect.

Fig.6. The tumor mass in the nasal septum revealed a poorly differentiated squamous cell carcinoma. HE.X100.

Fig.7. Location of the tumor mass in the left maxillary sinus.

Fig.8. The maxillary tumor was composed of fusiform and spindle cells having "squamoid" features (moderate differentiated squamous cell carcinoma). HE.X100. a

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