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Brain metastasis from differentiated thyroid cancer in patients treated with radioiodine for bone and lung lesions

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Brain metastasis of differentiated thyroid cancer (DTC) often is detected during treatment of other remote lesions. We examined the prevalence, risk factors and treatment outcome of this disease encountered during nuclear medicine practice. Of the 167 patients with metastasis to lung or bone treated 1–14 times with radioactive iodine (RAI), 9 (5.4%) also had lesions in the brain. Five were males and 4 females, aged 49–84, out of the original population of 49 males and 118 females aged 10–84 (mean 54.7) years. Three of them underwent removal of their brain tumors, 5 received conventional external beam irradiation, and 2 had stereotactic radiosurgery with supervoltage X-ray. None of the brain lesions showed significant uptake of RAI despite demonstrable accumulation in most extracerebral lesions. Seven patients died 4–23 (mean 9.4) months after the discovery of cerebral metastasis, brain damage being the primary or at least a contributing cause. The 8th and 9th patients remained relatively well for more than 42 and 3 months, respectively, without any evidence of intracranial recurrence. Our results confirmed that the brain is a major site of secondary metastasis from DTC. No statistically significant demographic risk factor was detected. Any suspicious neurological symptoms in the course of RAI treatment warrant cerebral computed tomography. As for therapy, from our initial experience, radiosurgery seemed promising as an effective and less invasive alternative to surgical removal.

Key words: thyroid cancer, radioiodine treatment, brain metastasis, bone metastasis, lung metastasis

INTRODUCTION

BRAIN METASTASIS from differentiated thyroid cancer (DTC) is uncommon but almost always fatal,[1–3] with its resistance to standard ways of treatment. Although in rare cases it can precede the diagnosis of primary tumor, it becomes apparent usually late in the clinical course, with rapid deterioration of the general condition. Since delay or failure in detecting cerebral metastasis during treatment to other remote lesions may result in a worse prognosis, knowing its prevalence and risk factors seems quite important. As an approach to this matter, we reviewed our case records of patients treated with radioactive iodine (RAI) for pulmonary and skeletal involvement. In addition, we will describe our experience with radiosurgery in 2 recent cases with brain involvement of DTC.

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PATIENTS AND METHODS

During the years 1981–1999, 167 patients with metastasis to lung, bone, or both, received I-131 therapy 1 to 14 times at the internal radiation facility in Kyoto University Hospital. Some of them also had other metastatic lesions in lymphnodes, skin, or liver, but since we are concerned with hematogenic cerebral metastasis, those with only local recurrence or nodal involvement were excluded. RAI was given in doses ranging 2.5–5.5 GBq (70–150 mCi) per session, after a preparatory period of iodine restriction and withdrawal of thyroid medication.[4] Among these, 9 (5.4%) also had brain metastasis in their clinical course (Table 1). The intracranial lesions in cases 6 and 8

Table 1 Clinical profiles of the patients with brain metastasis

	age* & sex	histology	interval** (years)	brain lesions	other metastasis	thyroglobulin* (ng/ml)
1	64M	papillary	3	lt frontal	lung	192.6
2	65M	follicular	1	rt parietal	bone & lung	n.d.***
3	64F	papillary	1	multiple	bone & lung	> 500
4	49M	papillary	1/2	multiple	lung	158.6
5	57M	follicular	10	lt occipital	lung	> 500
6	59F	papillary	8	cerebellum	lung	> 500
			9	multiple		
7	53M	papillary	6	lt parietal	bone & lung	> 500
			7	cerebellum		
8	61F	papillary	2	lt parietal	bone & scalp	> 500
9	84F	papillary	9	cerebellum	lung	29.6

* at the discovery of the (first) brain metastasis.
** between first thyroid surgery and discovery of brain metastasis.
*** not done.

Table 2 Therapy and prognosis of the patients with brain metastasis

	surgery	RAI (GBq)	external radiation	prognosis	registered main cause of death
1	—	3.7	50 Gy	died 9 mo*	respiratory failure (hemoptysis)
2	—	5.6 + 5.6	60 Gy	died 8 mo	systemic progression
3	—	3.7 + 4.4	50.4 Gy	died 6 mo	progression of brain lesions
4	—	3.0	50 Gy	died 7 mo	progression of brain lesions
5	removal	3.3	none	died 4 mo	neck recurrence and respiratory failure
6	removal**	3.7 + 3.3	50 Gy**	died 23 mo	respiratory failure (pleural effusion)
7	removal	4.4	none	died 9 mo	brain relapse
8	biopsy	3.3 + 4.8	radiosurgery	alive 42 mo	—
9	—	3.1 + 5.0	radiosurgery	alive 3 mo	—

* months after the discovery of the (first) brain metastasis.
** surgical intervention to the cerebellar lesion and radiation to the later lesions.

were found during computed tomography (CT) and/or magnetic resonance imaging (MRI) for metastasis in the skull and scalp. In 7 other cases, neurological symptoms such as headache, disorientation, gait disturbance or paralysis preceded the diagnosis of brain disease. Histological confirmation of cerebral lesion was obtained in cases 5–8, either at surgical removal (cases 5–7) or at biopsy (case 8). In the 5 remaining cases, brain metastasis was diagnosed clinically based on the characteristic appearances of the tumors in CT and/or MRI with marked perifocal edema and their progression over time.

Conventional external beam radiation applied to brain lesions employed supervoltage X-ray from a linear accelerator (LINAC) with daily fractions of 1.8 Gy. Stereotactic radiosurgery[5,6] to the last two patients was performed with narrowly collimated X-ray from a LINAC given in 5 arcs at a center dose of 25 Gy in a single session. This procedure is also known as X-knife.

As the tumor marker of DTC in athyreotic subjects, thyroglobulin (Tg) was measured in sera taken during thyroid replacement (hence without any effect due to high TSH levels), either by an in-house radioimmunoassay or with a commercial kit for immunoradiometric assay (7; Daiichi Radioisotope Laboratories, Tokyo, Japan), with good agreement between results of the two procedures. None of the patients with brain metastasis in this series had autoantibodies to human Tg.

Statistical analysis of numerical data was done with chi-square test, employing Yates' correction when appropriate.

RESULTS

Table 1 summarizes profiles of the 9 patients with brain metastasis. Neither the age nor sex ratio of this group differed statistically from the 158 subjects without cranial lesions, 44 males and 114 females aged 10–79 (mean 54.9) years. Histopathologically, papillary cancer (144 out of 158 cases without brain disease) predominated in both populations as a diagnosis of the original thyroid tumor.

Treatment and prognosis of the patients with brain metastasis are summarized in Table 2. All but two eventually died of thyroid cancer, with a mean survival time of

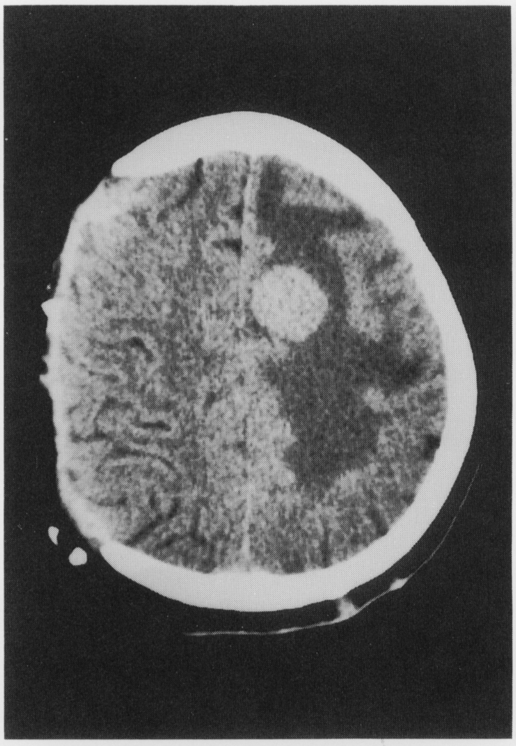

Fig. 1 Brain computed tomogram in case 8 demonstrates a round, high-density mass with marked perifocal edema in the left parietal region. Right parietal bone defect is due to previous craniotomy for biopsy.

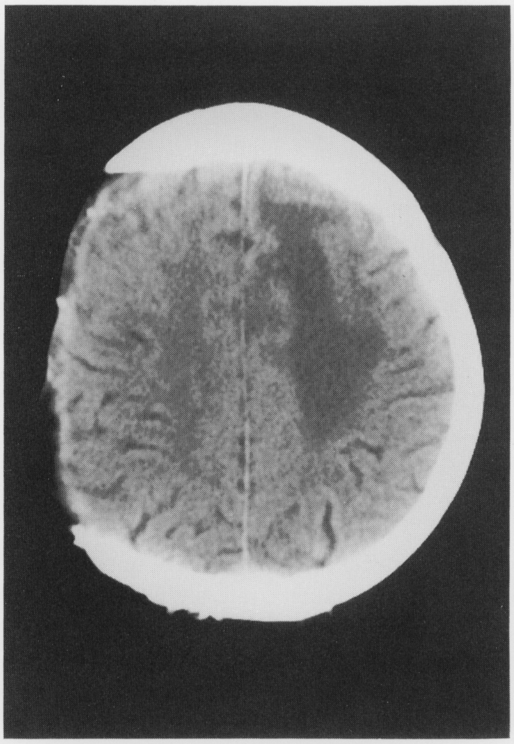

Fig. 2 Eight weeks after radiosurgery, the high-density mass seen in Figure 1 has disappeared and the edema reduced.

9.4 months after discovery of their brain disease. Surgical removal prolonged survival only in case 6, where an earlier single mass was successfully resected and progression of later multiple lesions was slowed down with irradiation. None of the intracranial lesions showed significant uptake of RAI, whereas concomitant lung and bone metastasis were positive in the post-therapeutic whole body scan except in cases 1, 6 and 9. Conventional radiotherapy in 5 subjects resulted in mass reduction or symptomatic relief, without any significant contribution to survival time other than in case 6 described above. Figures 1 and 2 show the therapeutic response to radiosurgery for the solitary metastasis in case 8. This patient remained relatively well for 42 months after diagnosis of the brain tumor, with slight clumsiness in her right hand and stable bone disease. Her latest head CT in April 1999 revealed a low density area similar to that shown in Figure 2, with no sign of recurrence in the metastatic tumor or emergence of new lesions. We are also closely following up the 9th patient who showed improvement in gait disturbance shortly after radiosurgery for the solitary lesion in her cerebellar vermis, expecting another local control with this mode of treatment.

DISCUSSION

Cerebral metastasis from DTC has been regarded as a rare disease. Indeed, its reported prevalence is around 1% among the whole population of surgically treated patients.[3,8,9] On the other hand, the brain was the most frequent locus of secondary metastasis from DTC in a study of a large cohort of patients.[10] That explains the relatively high proportion (5.4%) of intracranial involvement in our retrospective study, where only the subjects with lung or bone metastasis were included. We suppose all brain metastases described above to be hematogenic, since every focus appeared separate from the meninges on CT, even in cases with lesions in the skull or scalp. Our experience implies that in patients with blood-borne spreading, care should be taken to detect any cerebral complication as early as possible to minimize deterioration of the general condition. Any suspicious neurological signs and symptoms during clinical follow-up warrant brain CT or MRI to rule out this disease. In addition, emission computed tomography of the brain at the time of follow-up tumor scintigraphy (either with radiothallium or technetium-labeled agents) may detect unsuspected lesions.

Serum Tg was high in all but one of the patients with brain metastasis measured (Table 1), confirming differentiated nature of their thyroid cancer. Practically, however, it had been impossible in the clinic to suspect brain metastasis based only on high Tg values, since all the subjects already had distant metastasis elsewhere that could also produce and release Tg. Probably for the same reason, high serum Tg levels showed no clear tendency to fall after any therapy for intracranial lesions.

From the data obtained, we looked for potential demographic risk factors. Men slightly outnumbered women in the group with brain disease, but the sex ratio did not differ significantly in the rest of the RAI-treated subjects. Although the difference in the age of the two groups again failed to reach statistical significance, all the patients with brain lesions were 49 years of age or older, probably because distant metastasis of DTC in younger subjects occurs almost exclusively in the lungs. For that matter, in the 167 cases reviewed, the youngest patient with bone metastasis was 30 years old when that lesion was found.

The mean survival period of 9.4 months in 7 patients is worse than in other reports (11.7, 15, and 12.4 months in references 1, 2 and 3, respectively). This may be due to the difference in subject composition: whereas all the patients included here had systemic metastasis elsewhere besides the brain, some in the other 3 series did not have such lesions. We presume that a combination of cerebral involvement and progression in other distant foci may have accelerated the fatal outcome. Even in our cases 1, 2, 5 and 6, in addition to the recorded main causes of death, brain damage either from remaining cerebral implantation or from therapeutic interventions may have reduced food intake and expectorant reflex, thus shortening their survival period.

Because of its relatively radioresistant nature, the response of thyroid cancer to conventional external beam irradiation is modest at best. And only rarely does RAI accumulate in cerebral lesions from DTC,[3,11] presumably due to the blood brain barrier. Therefore, until recently, neurosurgical excision remained the most effective treatment with survival benefit,[3] though inapplicable to deep-seated tumors or in patients with serious concomitant medical problems such as cardiac failure or hepatic dysfunction. Meanwhile stereotactic radiotherapy has already been applied successfully to intracranial metastasis from other malignant tumors, such as hypernephroma and fibrosarcoma,[12] as well as to primary intracranial neoplasm and vascular anomaly.[13] With its ability to deliver a large dose to the target mass while minimizing damage to normal brain tissue, it could be applied to lesions made up of radioresistant cells. As for limitations, it needs a special guidance system to achieve stereotactic movement, and dedicated software for dose simulation; moreover, at one session it can only treat up to a certain number of (usually 3) lesions less than 3 cm in diameter, leaving the use of whole brain conventional irradiation to multiple or larger tumors. Our initial success in a patient with a parietal mass reassured us that this radiation procedure can control solitary or oligofocal cerebral metastasis from DTC.[6] We are following up the second patient hoping that this mode of therapy is also effective for her cerebellar lesion.

Although we could not find any demographic risk factor of statistical significance, our experience confirmed that brain metastasis is not so rare, more than 1 in 20, in patients who already have other remote metastasis from DTC. Radiosurgery seems an effective and less invasive alternative for this grave complication with a limited number of foci.

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