Annals of Nuclear Medicine Vol. 11, No. 2, 143–146, 1997

Scintigraphic visualization of ocular melanoma with Tc-99m glutathione

Ahmet TUTUŞ,*[1] Kuddusi ERKILIÇ,*[2] Meral T. ERCAN,*[4] Olgun KONTAŞ,*[3]
Mehmet AYDIN*[4] and Hakkı DOĞAN*[2]

*Departments of *[1]Nuclear Medicine, *[2]Ophthalmology and *[3]Pathology, Faculty of Medicine, Erciyes University, Kayseri, and Department of *[4]Nuclear Medicine, Faculty of Medicine, Hacettepe University, Ankara, Turkey*

In a patient with ocular melanoma scintigraphy obtained with ^{99m}Tc-GSH clearly demonstrated the histologically proven ocular lesion both in planar and SPECT images. ^{99m}Tc-sestamibi study obtained in the same patient three days later was negative. ^{99m}Tc-GSH is a potential alternative to the currently used radiopharmaceuticals for imaging both cutaneous and ocular melanomas and their metastases.

Key words: ^{99m}Tc-GSH, ^{99m}Tc-sestamibi, ocular melanoma

INTRODUCTION

SCINTIGRAPHIC DEMONSTRATION of ocular melanoma has been a challenge since first attempts at its localization with ^{32}P in 1952.[1] Later, other radiopharmaceuticals such as radioiodinated quinoline derivatives that have melanin affinity,[2] radioiodinated melanin precursors such as thiouracil,[3] N-isopropyl-p-[^{123}I]-iodoamphetamine (^{123}I-IMP) which is incorporated into melanin producing melanocytes,[4,5] and non-specific ^{67}Ga-citrate[6] have all been evaluated and have found limited routine use.

Radioimmunodetection of ocular melanoma with murine cutaneous anti-melanoma antibodies (AMab) has also been tested and found to be more effective when SPECT compared to planar imaging was used,[7–10] but widespread use of radiolabeled murine monoclonal antibodies or their fragments is restricted by the high cost of their commercial kits. In addition, they have prolonged blood clearance, high liver, spleen and bone marrow localization and may produce an antigenic reaction in human application.

^{99m}Tc labeled reduced glutathione (GSH) was proposed as a tumor imaging agent and first evaluated in head and neck tumors.[11] Later, in a comparative study in the detection of malignant melanoma metastases, the sensitivity and specificity were 91% and 95% with ^{99m}Tc-AMab and 84% and 90% with ^{99m}Tc-GSH, respectively, in a series of 43 patients,[12] but the only case of ocular melanoma in this series was detected with ^{99m}Tc-AMab, but not with ^{99m}Tc-GSH. We decided to reevaluate the uptake of ^{99m}Tc-GSH in ocular melanoma. There is ample evidence of the uptake of ^{99m}Tc-hexakis-2-methoxy-2-isobutyl isonitrile (sestamibi) by malignant tumors,[13] but its localization in ocular melanoma has not been reported. We, here, present a case of histologically confirmed ocular melanoma studied with both ^{99m}Tc- GSH and ^{99m}Tc-sestamibi.

CASE REPORT

A 60-year-old male was admitted to our hospital, because of gradually progressive reduction in visual acuity in the right eye, starting 2 years previously. The ophthalmological examination revealed absolute blindness, with no light perception in the right eye. There was a dark brown mass diffusely filling the subconjunctiva in the temporal bulbar quadrant. Ocular ultrasonography indicated a hypotonic right eye with hyper-echogenic high density areas in the vitreous body. X-ray computed tomographic examination revealed thickening of both temporal and posterior bulbus walls and diminished size of the right eye compared to the

Received November 20, 1996, revision accepted January 29, 1997.

For reprint contact: Prof. Dr. Meral T. Ercan, Department of Nuclear Medicine, Faculty of Medicine, Hacettepe University, 06100 Sıhhiye, Ankara, TÜRKİYE.

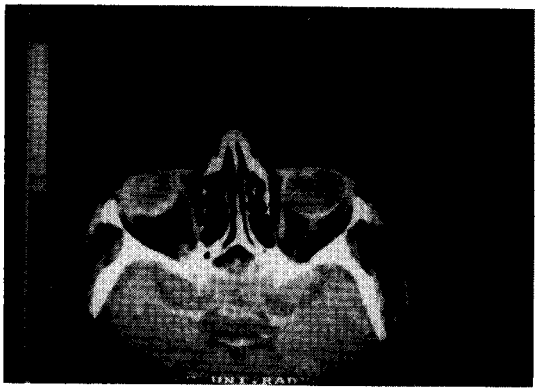

Fig. 1 The axial section of computed tomography of the orbit shows the smaller size of the right eye and the thickening of bulbus wall.

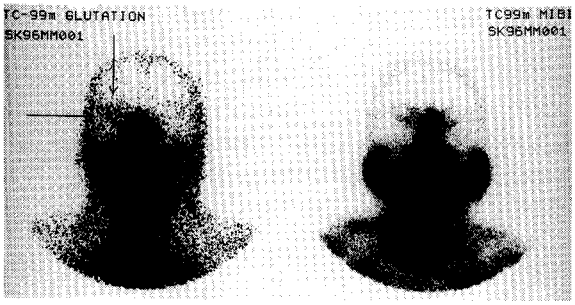

Fig. 2 Anterior planar images obtained with ^{99m}Tc-GSH at 3 h post-injection on the left and ^{99m}Tc-sestamibi at 45 min on the right in the same patient. There is increased accumulation of the tracer in the right eye with ^{99m}Tc-GSH. ^{99m}Tc-sestamibi study is negative.

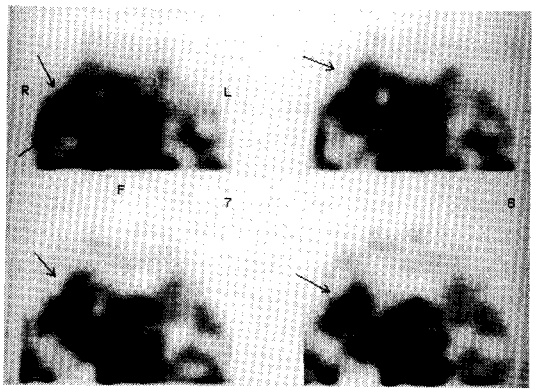

Fig. 3 Coronal slices obtained in the SPECT study with ^{99m}Tc-GSH clearly demonstrate the uptake by the tumor in the right eye.

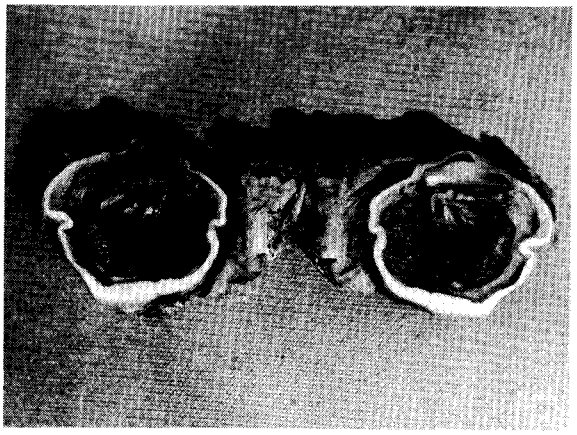

Fig. 4 Enucleated right eye sectioned in axial plane. Melanoma fills the vitreous cavity and extrascleral extension is also seen.

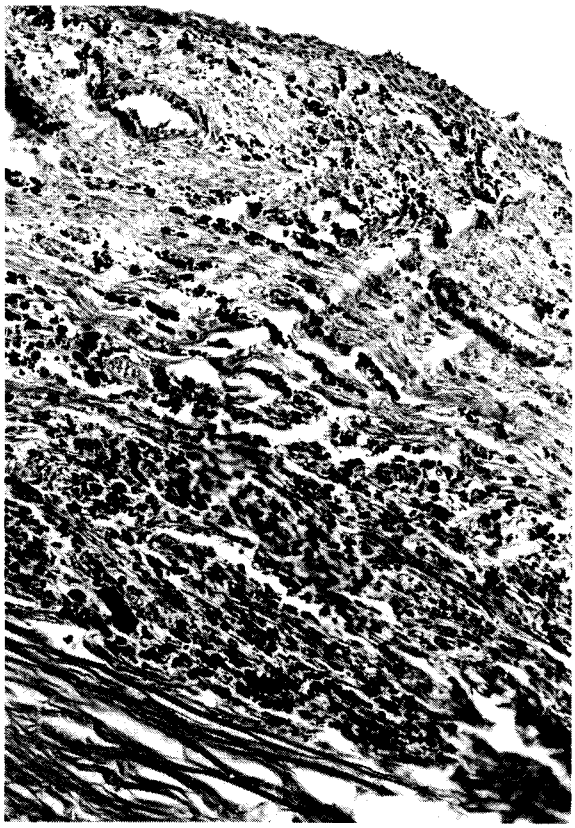

Fig. 5 Melanoma cells spread to the subconjunctival space by transversing sclera. Conjunctiva is upper right and sclera is lower left side of the picture. (Hematoxylin and Eosin, original magnification × 200).

left eye (Fig. 1). 555 MBq ^{99m}Tc-GSH prepared by previously published methods[11,14] was administered to the patient. Planar imaging with total counts of 500 k was performed at 3 h post-injection by using a LEAP collimator and a gamma camera (Toshiba GCA 602 A/SA, Japan). Scintigram in the anterior position demonstrated increased accumulation of radioactivity in the right compared to the left eye (Fig. 2). Following planar study SPECT was performed. The uptake by the tumor was also demonstrated in the coronal slices (Fig. 3). Three days later 555 MBq ^{99m}Tc-sestamibi (kit from Cardiolite, Dupont Company) was administered to the same patient and planar imaging was obtained 45 min later. There was no uptake by the lesion in the right eye (Fig. 2). The right eye

was enucleated, preserving the conjunctiva.

After fixation in 10% neutral buffered formalin and processing in absolute alcohol the globe was sectioned in the axial plane. The vitreous body was entirely filled with a dark brown-black colored tumor which contained necrotic areas. The choroid was diffusely thickened (Fig. 4).

In the histopathological examination there was a heavily pigmented, necrotic neoplastic tissue filling the vitreous cavity. Tumor cells had fusiform nuclei with small distinct nucleoli, and mitotic figures were uncommon. There were agglomerations of macrophages loaded with melanin pigment from the disrupted retinal pigment epithelium and necrotic tumor cells. Melanoma cells spread to the subconjunctival space by transversing sclera (Fig. 5).

DISCUSSION

We performed ^{99m}Tc-GSH and ^{99m}Tc-sestamibi scintigraphy in one patient with ocular melanoma. The high accumulation of ^{99m}Tc-GSH in the tumor was noted while ^{99m}Tc-sestamibi scintigraphy was negative. ^{99m}Tc-sestamibi was tested in this context for the first time; it needs to be further evaluated in a larger patient population. We reported another patient with ocular melanoma studied with ^{99m}Tc-GSH that did not accumulate in the tumor, but there was a diffuse uptake of ^{99m}Tc-anti-melanoma antibody (AMab).[12] This discrepancy might be attributed to GSH and GSH-related enzyme activities reported to be lower at sites of primary melanoma than in metastatic lesions,[15] variations in its amount in the tumor depending on the size, age and viability. Other factors might be the tumor size and lesion site which effect the sensitivity of detection. In the present investigation the tumor size was large. Here, SPECT would be more useful. Another possible application would be the imaging of metastatic lesions from ocular melanomas. This was successfully demonstrated with cutaneous melanomas.[12] Low uptake in the normal liver is an advantage, but considerable localization in the kidneys might obscure the metastatic lesions in the liver, but lesions at other areas could be detected. More patient studies are needed to demonstrate the efficacy of this new radiopharmaceutical in the diagnosis of ocular melanoma and its metastases.

The mechanism of uptake of ^{99m}Tc-GSH is not clear. Endogenous GSH in reduced form takes part in the detoxification processes. It functions through the sulfide group by reducing the oxidants and free radicals.[16] Due to increased metabolism of tumor cells, GSH might be depleted in cancer.[17,18] Its efficacy in the treatment of malignant tumors in experimental animals[19] might be explained by high GSH demand of malignant cells. GSH also plays an important role in melanin synthesis.[20,21] Flow cytometry has demonstrated high levels of GSH in human melanoma metastases. The mechanism of uptake of ^{99m}Tc labeled GSH might be explained by the above considerations, in addition to increased blood supply to the tumor and enhanced capillary permeability. Although ^{99m}Tc-GSH is a negatively charged water soluble complex, ^{99m}Tc-sestamibi is cationic and lipophilic in nature. It is accumulated within the mitochondria and cytoplasm of tumor cells due to increased transmembrane electrical potentials. It is also recognized by cytoplasmic membrane glycoprotein (Pgp) as a suitable transport substrate.[13]

Although many radiopharmaceuticals have been proposed for the scintigraphic delineation of malignant melanoma,[1-10] the results are not satisfactory. The only specific agent, ^{99m}Tc-AMab, has the disadvantages of high renal, slight liver, spleen and bone marrow localization, variable amounts of gallbladder and bowel radioactivity with prolonged blood clearance, in addition to the high cost of its kits. ^{99m}Tc-GSH has a sensitivity and specificity comparable to ^{99m}Tc-AMab.[12] The advantages of ^{99m}Tc-GSH are lower blood radioactivity levels, lower cost and easy in-house preparation. It is a potential radiopharmaceutical for the detection of ocular melanoma and its metastases.

REFERENCES

1. Thomas CI, Krohmer JS, Storaasli JP. Detection of intraocular tumors with radioactive phosphorus. *Arch Ophtalmol* 47: 276–286, 1952.
2. Beierwaltes WH, Varma VM, Liebermann LM, et al. Scintillation scanning of malignant melanomas with radioiodinated quinoline derivatives. *J Lab Clin Med* 72: 485–494, 1968.
3. Dencker L, Larsson B, Olander K, Ullberg S. A new melanoma seeker for possible clinical use: Selective accumulation of radiolabelled thiouracil. *Br J Cancer* 45: 95–104, 1982.
4. Holman BL, Wick MM, Kaplan ML, et al. The relationship of the eye uptake of N-isopropyl-p-[I-123]iodoamphetamine to melanin production. *J Nucl Med* 25: 315–319, 1984.
5. Ono S, Fukunaga M, Otsuka N, et al. Visualization of ocular melanoma with N-isopropyl-p-[I-123]-iodoamphetamine. *J Nucl Med* 29: 1448–1450, 1988.
6. Van Langevelde A, Bakker CNM, Boer H, et al. Potential radiopharmaceuticals for the detection of ocular melanoma. Part II. Iodoquinoline derivatives and ^{67}Ga-citrate. *Eur J Nucl Med* 12: 96–104, 1986.
7. Bomanji J, Garner A, Prasad J, et al. Characterization of ocular melanoma with cutaneous melanoma antibodies. *Br J Ophthal* 71: 647–650, 1987.
8. Bomanji J, Hungerford JL, Granowska M, et al. Radioimmunoscintigraphy of ocular melanoma with ^{99m}Tc labelled cutaneous melanoma antibody fragments. *Br J Ophthal* 71: 651–658, 1987.
9. Scheidauer K, Markl A, Leinsinger MG, et al. Immunoscintigraphy in intraocular malignant melanoma. *Nucl Med Commun* 9: 669–679, 1988.
10. Liewendahl K, Pyrhönen S. Radioimmunodetection and radioimmunotherapy of malignant melanoma. *Acta Oncologica* 32: 717–721, 1993.
11. Ercan MT, Aras T, Aktaş A, et al. Accumulation of ^{99m}Tc-glutathione in head and neck tumors. *Nucl-Med* 33: 224–228, 1994.

12. Duman Y, Burak Z, Ercan MT, et al. Clinical evaluation of metastases of malignant melanoma imaging with Tc-99m-glutathione and Tc-99m-anti-melanoma antibody: A comparative study. *Nucl Med Commun* 16: 927–935, 1995.
13. Abdel-Dayem HM, Scott AM, Macapinlac HA, et al. Role of Tl-201 chloride and Tc-99m sestamibi in tumor imaging. *In* Freeman LM (ed.): Nuclear Medicine Annual 1994, New York, Raven Press Ltd., pp. 181–234, 1994.
14. Ercan MT, Bekdik CF, Şarizi T. Tc-99m-glutathione: labelling and distribution in rats. *Int J Appl Rad Isotopes* 29: 697–698, 1978.
15. Chakraborty AK, Ueda M, Mishima Y, Ichihashi M. Intracellular glutathione and its metabolizing enzyme activities in a metastatic variant melanoma cell line. *Melanoma Res* 2: 315–319, 1992.
16. Reed DJ. Regulation of reductive processes by glutathione. *Biochem Pharmacol* 35: 7–13, 1986.
17. Reed DJ. Glutathione: toxicological implications. *Ann Rev Pharmacol Toxicol* 30: 603–631, 1990.
18. Reed DJ, Fariss MW. Glutathione depletion and susceptibility. *Pharmacol Rev* 36: 25–33, 1984.
19. Novi AM. Regression of aflatoxin B_1-increased hepatocellular carcinomas by reduced glutathione. *Science* 212: 541–542, 1981.
20. Coates A, Tripp E. Glutathione content of human malignant melanoma cell lines: correlation of flow cytometric and biochemical assays and application to human tumor aspirates. *Melanoma Res* 1: 327–332, 1992.
21. Mannervik B, Castro VM, Danielson VH, et al. Expression of class Pi glutathione transferase in human malignant melanoma cells. *Carcinogenesis* 8: 1929–1932, 1987.