Early Changes in Fluorine-18-FDG Uptake During Radiotherapy

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The aim of this case study was to quantify metabolic changes in tumor tissue during and directly after external radiotherapy. **Methods:** We performed six FDG-PET scans of the neck in a patient with two lymph node metastases of a papillary thyroid carcinoma and an antigranulocyte antibody scintigraphy of the same region to assess the inflammatory reaction. **Results:** The FDG-PET scans show an initial increase of tracer uptake in both metastases after application of 6 Gy followed by a slow but constant decline with increasing radiation dose. In the deep metastasis the FDG uptake returned to the initial level after 30 Gy total dose whereas the metabolic activity in the superficial lymph node remained high, even after 60 Gy total dose. The antigranulocyte scan demonstrated an intense inflammation in the latter metastasis. **Conclusion:** There is an initial enhancement in metabolism induced by irradiation which is measureable by FDG-PET. With increasing dose, the metabolic activity declines constantly. The additional inflammatory reaction might contribute to the glucose uptake in irradiated tumors.

Key Words: neoplasm; inflammation; radiotherapy; tomography; emission-computed; glucose metabolism

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The glucose consumption in cancer cells increases with the grade of malignancy (*1–3*). This is visualized by PET using ^{18}F-2-fluoro-2-deoxyglucose (FDG) as a measure of glucose metabolism (*2–4*). After successful radiotherapy, the metabolic activity in tumors decreases in comparison to the pretherapeutic state (*5*). We investigated the metabolic reaction of two cervical lymph node metastases in a patient with papillary thyroid carcinoma during radiotherapy to assess early changes in glucose metabolism.

CASE REPORT

A 65-yr-old male presented with two left-sided cervical lymph node metastases of a papillary thyroid carcinoma. First diagnosed in 1992, the patient underwent a total thyroidectomy and left-sided neck dissection followed by ^{131}I therapy. In April 1993, the patient presented with a first recurrence in a left retroauricular lymph node. This metastasis was surgically removed. Two other recurrences were removed at the same site in August and December 1994. Thereafter the patient was referred for radiotherapy because of two unresectable lymph node metastases near the base of the skull. A total dose of 60 Gy was applied in fractions of 2 Gy per day over a period of 7 wk. The superficial metastasis became inflamed during the radiotherapy. Since the inflammation of the superficial metastasis was clinically obvious, radiotherapists refused a biopsy to avoid additional irritation at the site of irradiation.

The outcome of the treatment was staged with radiography computed tomography as no change in the superficial and a partial response in the deep metastasis.

The patient died a few weeks after the completion of the radiotherapy due to disseminated lung metastases.

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Before and during irradiation, six FDG-PET scans were performed to assess the immediate changes in glucose metabolism caused by the ongoing radiotherapy (Fig. 1).

The FDG-PET scans were conducted while the patient was fasting. Between 250 and 346 MBq FDG were injected intravenously as a bolus. Imaging started immediately after injection using a four-ring (4.6 cm), seven-plane Scanditronix PC 4096/7 WB scanner with a FWHM of 7 mm. The patient was scanned in two contiguous positions starting from the orbito-meatal line downwards. Transmission scans were obtained by using a ^{68}Ga source. Static images used for analysis represent emission data collected 30 to 90 min after FDG administration. Data acquisition was performed for 30 min at each position. The emission scans were reconstructed iteratively.

The FDG uptake was expressed as a maximal differential uptake ratio (DUR) corrected for the partial volume effect (*6*).

The initial uptake ratio was 6.1 DUR in the superficial metastasis and 6.2 DUR in the deep metastasis, respectively. Both metastases showed an uptake enhancement: the superficial metastasis to 11.6 DUR (89% increase) and the deep metastasis to 10.1 DUR (65% increase). This initial increase was followed by a constant decline during treatment in both cases (Fig. 2). The deep metastasis declined to its original level after 30 Gy of total dose and continued to decrease to 3.8 DUR after radiotherapy. The metabolism of the superficial metastasis never returned to the initial uptake, even after 60 Gy of total dose. It remained elevated at 7.5 DUR.

Because of a clinical inflammation in the superficial metastasis and an increased FDG uptake in both metastases, an antigranulocyte scintigraphy was performed after 41 Gy superficial and 48 Gy deep irradiation dose, respectively, using an antigranulocyte BW 250/183 kit (Behringwerke, Marburg, Germany). This approach was chosen because of its high accuracy and sensitivity in detecting soft-tissue infections (*7*). Planar and SPECT scans were obtained 24 hr after injection of 862 MBq ^{99m}Tc-labeled antibodies using a Prism 2000 double headed gamma camera (Picker International, Bedford Heights, OH). The scans showed an intense accumulation of antibody-labeled granulocytes in the superficial metastasis in contrast to minimal uptake in the deep metastasis (Fig. 3).

DISCUSSION

Investigations of the impact of irradiation on the glucose metabolism show a decrease of FDG uptake in radiosensitive tumors (*5,8*). However, no investigations focused on the very early changes during radiotherapy.

In the present case, the initial increase in glucose metabolism seems to be triggered by irradiation. According to these findings, small amounts of radiation increase the glucose uptake in tumors due to an elevation in its metabolic level.

The agglomeration of the antigranulocyte antibody BW 250/183 in the superficial metastasis but not in the deep metastasis exhibits either an inflammation or—as a consequence of the antibody cross-reactivity—the expression of carcinoembryonic antigen (CEA), which is present in up to 30% of papillary carcinomas (*9*). Since the inflammation was clini-

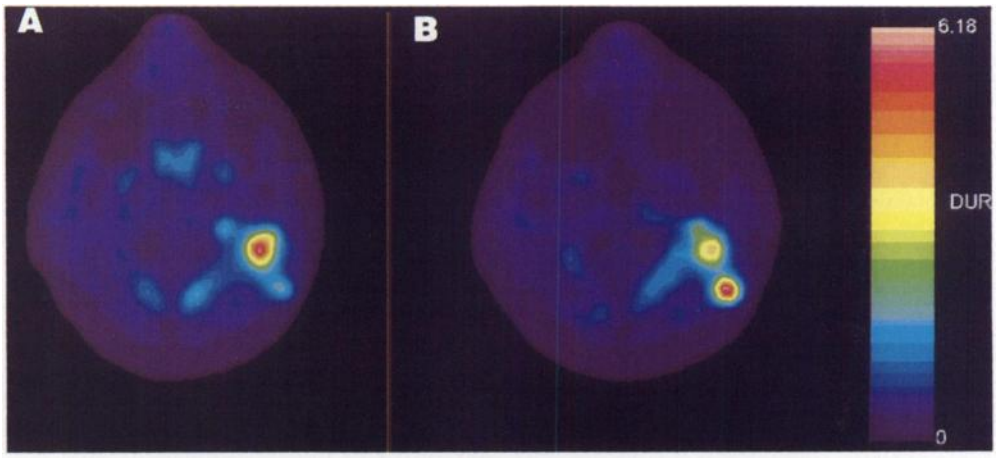

FIGURE 1. (A) Left cervical deep metastasis before radiotherapy. (B) Superficial metastasis left cervical before radiotherapy. Note also part of the deep metastasis.

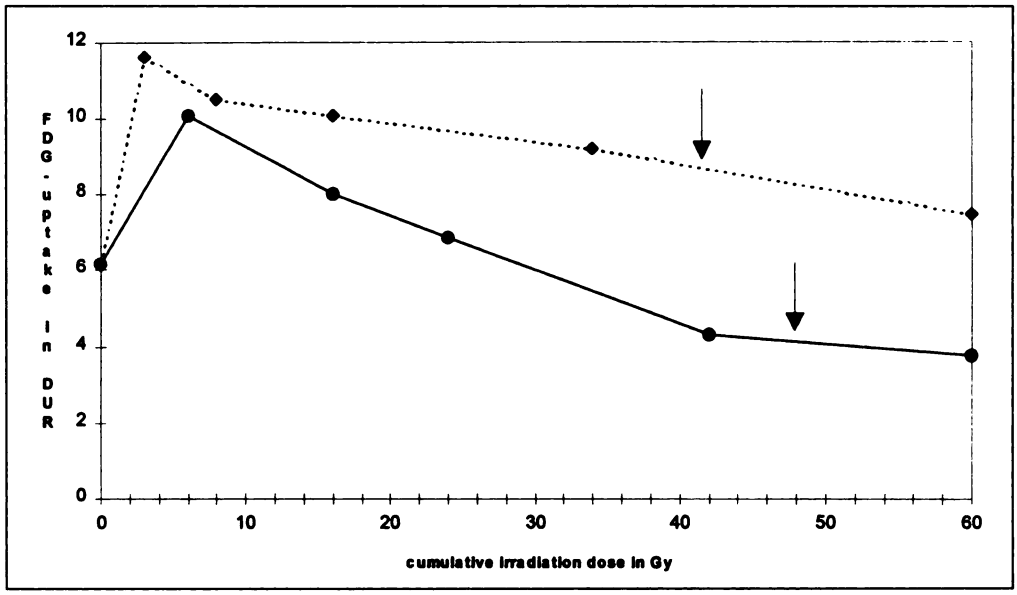

FIGURE 2. FDG-uptake in the deep metastasis (—) and the superficial metastasis (····) before and during radiotherapy (total dose 60 Gy). Depending on irradiation plans, cumulative dose was not equal in both metastases on days of PET investigations. FDG uptake measurements were done after 3 Gy, 8 Gy, 16 Gy, 34 Gy and 60 Gy in the superficial and after 6 Gy, 16 Gy, 42 Gy and 60 Gy in the deep metastasis. ↓ indicates actual dose in the deep and the superficial metastasis at the point of performing the antibody scan.

cally obvious the differential diagnosis of CEA expression is less probable.

This inflammation in the superficial metastasis may result in a contribution to the total uptake. Tahara et al. (*10*) reported that FDG uptake in inflamed tissues can be as high as in malignancies. Minn et al. (*11*) report that cancer is often obscured by inflammation and other changes. Furthermore, at least part of the elevated FDG uptake might be due to the minimal response of both metastases to treatment.

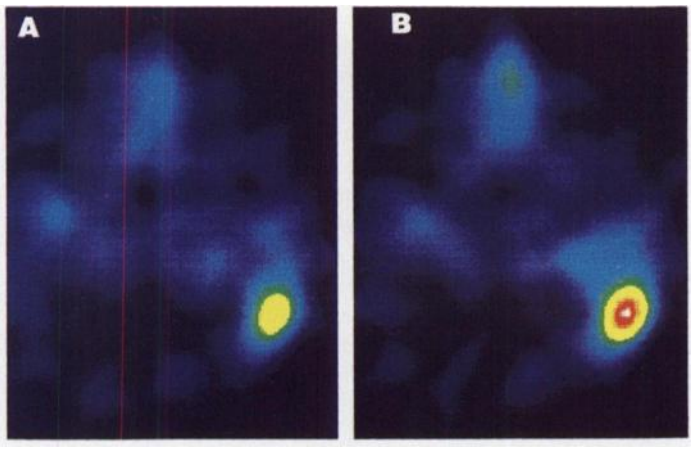

FIGURE 3. Antigranulocyte antibody scintigraphy. Transversal SPECT scans 24 hr postinjection. Corresponding slices to Figure 1. Note the intense tracer accumulation in the superficial metastasis whereas the activity at the location of the second metastasis, which is located more anterior and medial towards the center of the head, does not exceed the activity of the contralateral region.

The difference in changes of FDG uptake in the two lesions during radiotherapy appears to be caused by the additional influence of the inflammatory process in the superficial metastasis. A partial response to treatment of the neoplastic cells in the superficial node might be present. However, the effect on FDG uptake is obscured by the inflammation. These two factors cannot be separated precisely.

Support on irradiation induced increase for FDG and glucose metabolism is given by in vitro studies. Higashi et al. (*12*) found a 9.7-fold increase in FDG uptake in a human ovary adenocarcinoma cell line, measuring metabolic rates 0 to 12 days after irradiation with 30 Gy. By irradiating human glioblastoma cells, Schneeweiss et al. (*13*) found an increased FDG uptake of 11.3% compared to controls.

CONCLUSION

Low-dose irradiation may enhance tumor glucose uptake, and inflammatory changes may contribute to this increase. Performing FDG-PET scans during and directly after radiotherapy may therefore not yield accurate information about treatment response.

Systematic prospective studies are warranted to understand early metabolic changes in tumors during radiotherapy, to assess

the role of irradiation induced inflammatory reaction and, finally, to identify tumor response to treatment at a very early stage.

REFERENCES

1. Warburg O. The metabolism of tumors. London: Arnold Constable 1930;75–327.
2. Hatazawa J, Bairamian D, Fishbein DS, Brooks RA, Di Chiro G. Glucose utilization of non-gliomatous cerebral neoplasms as an index of tumor aggressivity [Abstract]. *J Nucl Med* 1986;27:901.
3. Di Chiro G, Hatazawa J, Katz DA, Rizzoli HV, De Michele DJ. Glucose utilization by intracranial meningiomas as an index of tumor aggressivity and probability of recurrence: a PET study. *Radiology* 1987;164:521–526.
4. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med* 1991;32:623–648.
5. Ichiya Y, Kuwabara Y, Otsuka M, et al. Assessment of response to cancer therapy using ^{18}F-FDG and PET. *J Nucl Med* 1991;32:1655–1660.
6. Woodard HQ, Bigler RE, Freed B, Russ G. Expression of tissue isotope distribution. *J Nucl Med* 1975;16:958–959.
7. Corstens FHM, Oyen WJG, Becker WS. Radioimmunoconjugates in the detection of infection and inflammation. *Semin Nucl Med* 1993;23:148–164.
8. Minn H, Paul R, Ahonen A. Evaluation of treatment response to radiotherapy in head and neck cancer with ^{18}F-FDG. *J Nucl Med* 1988;29:1521–1525.
9. Schroder S, Kloppel G. Carcinoembryonic antigen and nonspecific cross-reacting antigen in thyroid cancer. An immunocytochemical study using polyclonal and monoclonal antibodies. *Am J Surg Pathol* 1987;11:100–108.
10. Tahara T, Ichiya Y, Kuwabara Y, et al. High [^{18}F]-fluorodeoxyglucose uptake in abdominal abscesses: a PET study. *J Comput Assist Tomogr* 1989;13:829–831.
11. Minn II, Aitasalo K, Happonen RP. Detection of cancer recurrence in irradiated mandible using PET. *Eur Arch Otorhinolaryngol* 1993;250:312–315.
12. Higashi K, Clavo AC, Wahl RL. In vitro assessment of 2-fluoro-2-deoxy-D-glucose, L-methionine and thymidine as agents to monitor the early response of a human adenocarcinoma cell line to radiotherapy. *J Nucl Med* 1993;34:773–779.
13. Schneeweiss FHA, Sharan RN, Hautzel H, Rüb T, Müller-Gärtner H-W. Effect of ionizing radiation on conversation factor between deoxyglucose and glucose (lumped constant) in human glioblastoma cells in vitro [Abstract]. *J Nucl Med* 1995;36:202.

Thallium-201 Uptake in Cytomegalovirus Encephalitis

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A 36-yr-old man with AIDS exhibited intense ^{201}Tl uptake (lesion-to-brain uptake ratio 5.38) in a brain lesion previously detected by MRI and CT. The lesion was biopsied and found to contain cells with viral inclusions diagnostic of cytomegalovirus infection, not tumor as the thallium SPECT results suggested. Thallium-201 SPECT may be less specific than previously reported for differentiating neoplastic disease from opportunistic infections in AIDS patients.

Key Words: thallium-201; SPECT; AIDS; cytomegalovirus

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Central nervous system (CNS) complications associated with Acquired Immune Deficiency Syndrome (AIDS) cause significant morbidity and mortality. Etiologies of CNS disease in AIDS include neoplasms and opportunistic infections. In one autopsy study, CNS lymphoma was found in 4% of AIDS patients (*1*). Autopsy incidence of 6.7%–34% has been reported for cerebral toxoplasmosis (*1*). Other common infections include: cytomegalovirus (CMV) (7.9%–33%), cryptococcosis (2.6–13.5%) and progressive multifocal leukoencephalopathy (0.8%–8%) (*1*).

Since CNS complications commonly occur in AIDS and the consequences are severe, rapid diagnosis leading to proper treatment might enhance the quality of life in these patients. Specific diagnosis of CNS complications is unreliable with MRI or CT since the imaging characteristics of lymphoma and opportunistic infections can be similar (*2,3*). The use of ^{201}Tl SPECT to differentiate between CNS lymphoma and infectious diseases in AIDS patients has been reported previously (*4–7*). In those studies, lymphomas showed increased thallium uptake, while infectious diseases generally did not. In this case, we report ^{201}Tl uptake in a biopsy and autopsy-confirmed case of CMV encephalitis.

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CASE REPORT

The patient, a 36-yr-old man with AIDS, was admitted with progressive neurological complaints, including left hemiparesis and an increased occurrence of falls. Past medical history included *Pneumocystis carinii* pneumonia and *Mycobacterium avium* infection. The patient was enrolled in an oral gancyclovir prophylaxis trial until the month of admission.

Neurological exam revealed mild psychomotor slowing, decreased facial sensation to pinprick and mild paresis of the lower extremity on the left side. Left upper extremity drift, mild graphesthesia and marked paresis were noted. Three months before admission, the patient was noted to have a "lazy left upper lip". A CT without contrast showed right thalamic and periventricular edema, mild hydrocephalus and mild atrophy. Based on these findings, the patient was started empirically on an anti-*Toxoplasma gondii* regimen (pyrimethamine tablets 25 mg bid, intravenous clindamycin 600 mg tid). MRI revealed a right basal ganglia lesion, extending inferiorly to the level of the right mid brain and superiorly to the level of the right corona radiata (Fig. 1). Three days after the initiation of anti-toxoplasma medication, ^{201}Tl SPECT brain imaging was performed. Thallium-201 uptake was shown in the right frontal/parietal region on both early and delayed acquisitions (Fig. 2). After 2 wk of anti-toxoplasma medication, an MRI with gadolinium showed a ring-enhancing lesion in the right basal ganglia unchanged from the previous study in size or mass effect. Because lymphoma was suspected, the patient underwent a stereotactic brain biopsy. The biopsy revealed cytomegalovirus encephalitis and subacute organizing infarction. To treat the CMV infection, the patient was started on intravenous gancyclovir 300 mg twice a day. After 1 wk without change in the patient's left hemiparesis and a decrease in platelet count, gancyclovir was discontinued and intravenous foscarnet 5 gm twice a day was initiated. A CT at this time showed no significant change in the lesion. After 3 days of foscarnet therapy, left side mobility had increased. Eight days after the initiation of foscarnet therapy, MRI with gadolinium showed, as