Permanent iodine-125 (125I) brachytherapy has been shown to improve local control after the resection of malignant brain tumors. Reported complications of such implantations have included delayed cerebral edema and radiation necrosis. A much less studied, yet anecdotally reported, complication is seed migration from the initial site of implantation. Migration of 125I seeds within the cerebrospinal fluid has been described after brachytherapy for recurrent glioblastoma located in the periventricular region.

A unique case of seed migration occurred within the brain parenchyma after permanent 125I seed implantation for metastatic brain tumor. Covering a 7-year follow-up period, we discuss the speed and course of seed migration along the white matter tracts, speculating about the possible causes in this patient with a known nickel allergy and previous reaction to titanium.

This case report documents the migration of 3 iodine-125 (125I) seeds from the tumor resection cavity into brain parenchyma over a 7-year period. A 66-year-old woman had a history of metastatic ovarian carcinoma, nickel allergy, and reaction to a titanium hip implant that required reoperation for hardware removal. In this unique case of parenchymal migration, the seed paths seemed to follow white matter tracts, traveling between 18.5 and 35.5 mm from the initial implant site. The patient’s initial neurological decline, which was thought to be related to radiation necrosis, appeared to stabilize with medical therapy. She subsequently developed progressive right hemispheric edema that resulted in neurological deterioration and death. Considering her previous reactions to nickel and titanium, the authors now speculate that her later clinical course reflected an allergic reaction to the titanium casing of the 125I seeds. Containing a trace amount of nickel, 125I seeds can elicit a delayed hypersensitivity reaction in patients with a history of nickel dermatitis. Preoperative patch testing is recommended in these patients, and 125I seed implantation should be avoided in those who test positive.

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Case Report

Previous Treatment

A 66-year-old woman with a history of metastatic ovarian carcinoma underwent suboccipital craniectomy and resection of a right cerebellar metastasis with the implantation of Gliadel wafers followed by fractionated radiation. Two years later, following craniotomy and resection of a right anterior frontal metastasis, she had stereotactic radiosurgery to both the right anterior frontal resection cavity and a second metastatic tumor in the right motor cortex.

Permanent 125I Seed Implantation

Four years later, when the patient presented with left leg weakness and gait imbalance, MRI demonstrated an 8 × 11-mm enhancing lesion in the right motor cortex at the site of previous radiosurgery (Fig. 1A). Positron emission...
tomography with FDG showed increased uptake consistent with recurrent metastatic tumor. We recommended proceeding with tumor resection and permanent $^{125}$I seed implantation. The patient had a history of nickel allergy and an allergic reaction to a titanium hip implant that had required a second operation for hardware removal. She was counseled that a trace amount of nickel in the titanium casing of the seeds could evoke an allergic response in the brain. We offered resection followed by stereotactic radiosurgery as an alternative approach; however, the patient wished to proceed with $^{125}$I seed placement because the previous course of radiosurgery had not controlled the tumor.

After craniotomy and resection of tumor in the right motor area, 7 $^{125}$I seeds (0.683 mCi, OncoSeed, model no. 6711, Oncura/GE Healthcare) were inserted to a 5-mm depth into the brain surrounding the resection cavity at a prescribed dose of 150 Gy (Fig. 1B). The cavity was covered with Surgicel (Ethicon) and Tisseel (Baxter) to prevent dislodgement. The pathology report confirmed metastatic adenocarcinoma with papillary features. The patient had an uneventful postoperative course, did not experience any deterioration in motor function, and underwent evaluation every 3–6 months by neurological examination and MRI.

$^{125}$I Seed Migration

Two years after resection and seed implantation, follow-up MRI revealed increased enhancement along the medial margin of the resection cavity. The patient was neurologically stable (Karnofsky Performance Scale [KPS] Score 90) and was started on pentoxifylline (Trental) and vitamin E for presumptive radiation necrosis. Over the next 4 years, we tracked the migration of 3 $^{125}$I seeds from the resection cavity into the brain parenchyma (Fig. IC–F and Table 1). When the first migrating seed was detected 3 years after seed implantation, the patient had remained at her neurological baseline (KPS Score 90). Five years after seed implantation, when a second seed had migrated from the resection cavity into the brain parenchyma, she exhibited increasing gait imbalance and used a walker (KPS Score 60). Magnetic resonance imaging revealed stable enhancement along the resection cavity and new white matter edema thought to be consistent with the progression of radiation necrosis. The patient was started on dexamethasone (Decadron).

Six years after seed implantation, the patient was started on levetiracetam (Keppra) after suffering a left focal motor seizure. Now MRI showed continued migration of the first 2 seeds, new migration of a third seed, and markedly progressed edema of the right hemisphere without any change in the enhancement of the resection cavity. We contemplated surgical removal of the migrating seeds. Given that the 3 seeds had migrated along the corticospinal tract, we felt that seed retrieval would result in permanent hemiplegia so it was not undertaken. The patient deteriorated neurologically, experiencing increasingly frequent left focal motor seizures that resulted in left hemiplegia. She entered hospice care and died 7 years after the radiation seed implantation.

$^{125}$I Seed Migration Kinetics and Composite Radiation Dose

Follow-up MRI scans were fused to the immediate postimplant scan using the BrainLab iPlan RT Image software. The root-mean-square distance traveled between sequential scans was divided by the time interval between scans to obtain velocity measurements and the total distance traveled. The 3 seeds appeared to migrate along white matter tracts with an average velocity of 8.9 mm/year. The maximum velocity was highest for Seed 2 (11.5 mm/year). On the last imaging study, Seeds 1, 2, and 3 had migrated 28.8, 35.5, and 18.5 mm, respectively, from the resection cavity. The seeds began migrating approximately 3 years after surgery when 99.9997% of the radiation dose had already been delivered. Composite dose analysis revealed that a negligible dose of radiation (0.8 cGy) was delivered to the brain by the 3 seeds over the entire period of seed migration.

Discussion

Our case report documents the migration of 3 $^{125}$I seeds from the tumor resection cavity into the brain parenchyma.
TABLE 1. Iodine-125 seed migration within a patient’s brain parenchyma during a 7-year period

<table>
<thead>
<tr>
<th>Seed No.</th>
<th>Average Velocity (mm/yr)</th>
<th>Total Distance From Initial Implantation Site (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.3</td>
<td>28.8</td>
</tr>
<tr>
<td>2</td>
<td>11.5</td>
<td>35.5</td>
</tr>
<tr>
<td>3</td>
<td>6.0</td>
<td>18.5</td>
</tr>
</tbody>
</table>

over a 7-year period. In this unique case of parenchymal migration, the seed paths seemed to follow white matter tracts, traveling between 18.5 and 35.5 mm from the initial implant site (Table 1). The patient’s initial neurological decline was thought to be related to radiation necrosis and appeared to stabilize with medical therapy. She subsequently developed progressive right hemispheric edema that resulted in neurological deterioration and death. Considering her previous nickel allergy and reaction to titanium implants, we now speculate that her later clinical course reflected an allergic reaction to the titanium casing of the 125I seeds.

Etiology of Seed Migration

125I seed migration is common after brachytherapy outside the brain. Up to 25% of patients undergoing prostate brachytherapy will have radiographic evidence of 125I seed migration to various organs. The mechanism appears to be embolization via regional veins with transport through the right heart to the lungs. In contrast, we found only 1 report of 125I seed migration after brachytherapy in the brain; specifically, Larson et al. described seeds that migrated through the ventricular system in a patient after implantation for recurrent periventricular glioblastoma.

We believe that our case is the first reported instance of parenchymal seed migration after permanent 125I seed implantation for malignant brain tumor. Unlike the vascular and ventricular systems, the brain parenchyma should offer a high level of resistance to seed migration. Our patient demonstrated radiographic changes consistent with early radiation necrosis 2 years after seed implantation, and the first seed migrated 1 year later. Although it is possible for the seed migration to have been initiated by the radiation necrosis, one would expect the general incidence of seed migration to be much higher, in fact, corresponding with the 6%–23% incidence of radiation necrosis in studies of permanent 125I seed implantation for brain metastasis. Ultimately, the initiating and sustaining mechanisms of parenchymal seed migration in our patient remain uncertain.

Clinical Impact of Nickel Allergy

Our patient developed progressive right hemispheric edema that was out of proportion to the relatively stable enhancement at the resection cavity; additionally, it appeared to increase with each subsequent seed that migrated to the white matter. It is unlikely that the white matter edema was the result of radiation injury from the migrating seeds. Composite dose analysis confirmed that only 0.8 cGy was delivered to the brain by the migrating seeds, representing a fraction of the radiation dose delivered by 1 head CT scan (2.34–3.78 cGy). Considering the patient’s previous nickel allergy and reaction to titanium implants, we hypothesized that the expanding white matter edema reflected a hypersensitivity reaction to the alloy of the titanium seed casing. The 125I seeds implanted in our patient are commonly used for permanent brachytherapy in the brain and other body sites. The casing is a welded titanium alloy that contains up to 0.03% nickel by weight (American Society for Testing and Materials International B338 specifications).

There is ample evidence that titanium implants can evoke a delayed hypersensitivity reaction in patients with a history of nickel allergy. Cutaneous reactions after hip implants appear within weeks to months. In contrast, deep tissue inflammatory reactions have been reported up to 6 years after hip implant. In 1 study, histological analysis of tissue surrounding the titanium implant showed a cellular infiltrate consisting of lymphocytes and macrophages. Two recent case reports have documented hypersensitivity reaction of the brain to nickel-containing aneurysm clips.

In a similar way, we believe that the 3 migrating seeds in our patient precipitated a hypersensitivity reaction to the nickel-containing alloy that resulted in progressive white matter edema, neurological deterioration, and death. The time course of our patient’s symptoms and radiographic changes were within the timeframe of reported cases in the orthopedic literature. Although this hypothesis was not proven by histological analysis or a reversal of symptoms after implant removal, it is the most likely explanation for the radiographic and clinical findings.

Conclusions

This unique case of parenchymal seed migration after 125I seed implantation for brain metastasis had a mechanism of migration within the white matter that could not be elucidated. Patients undergoing permanent 125I seed implantation should be counseled about the possibility of seed migration within the cerebrospinal fluid or brain parenchyma. 125I seeds contain a trace amount of nickel that can elicit a delayed hypersensitivity reaction in patients with a history of nickel dermatitis. Preoperative patch testing is recommended in these patients, and 125I seed implants should be avoided in patients who test positive.

References

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**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Warnick, Breneman. Acquisition of data: Warnick, Brahimaj, Lamba. Analysis and interpretation of data: Warnick, Lamba, Breneman. Drafting the article: all authors. Critically revising the article: Warnick, Lamba, Breneman. Reviewed submitted version of manuscript: all authors. Study supervision: Warnick, Breneman.

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