From the NMRO President

Welcome to the summer edition of the Scintillator! We’ve had a successful past year and are excited about the opportunities this year will bring. As a wrap-up for the year, we had our annual NMRO networking luncheon at the SNMMI annual meeting, followed by a relaxed and more social happy hour. Our luncheon topic this year was government relations and politics, with a review of the ACGME Next Accreditation System. Both events were successful, and if you did not attend, I encourage you to do so next year. I had the good fortune to meet many different residents from both domestic and international programs whom I will see again and maybe collaborate with in my future career. We had recently opened membership to international residents, and the enthusiasm was exciting. In our next issue, Dr. Sachpekidis will be sharing with us the differences and similarities in nuclear medicine training between Europe and the US. NMRO is an international organization, and we want to be able to provide more—whether it is education, networking, or involvement with health policy. In that regard, I remind members to continue to be active, to get involved, and to remember that we are all one community with very similar interests and goals. With that, I’d like to congratulate our newest board members:

NMRO BOARD OF DIRECTORS

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- Anthony Fotenos, MD, PhD, NMRO Intern, Johns Hopkins

This year we have a lot planned for our residents. We will be publishing the Scintillator quarterly. If you have an interesting topic, please contact us to be included in the next issue. Additionally, we will continue our tradition of providing clinically relevant virtual journal clubs, with the next one slated for the fall. This is a good opportunity to join us during your program’s noon conference, as we will include a Q&A session with industry experts. Some having made our way in this column through spring 2013’s bumper crop for radiopharmaceuticals at the FDA (Lymphoseek, Xofigo, AdreView), it’s time to update readers on what’s new in the interim. On March 27, 2014, the Centers for Medicare & Medicaid Services (CMS) confirmed its noncoverage decision for amyloid PET, meaning most patients seeking to narrow a differential diagnosis containing Alzheimer’s get to choose between (1) paying out-of-pocket to have their brains stained with a Congo-red–like radiotracer while alive or (2) dying, the tried-and-true method since Alois Alzheimer looked under the microscope at Auguste D’s brain and described widespread “miliary foci” in his pathology report of 1907.

My purpose here, however, is to review why the FDA approved three new amyloid PET tracers, not why CMS won’t pay for them. Essentially, the reason goes back to 1907 and those miliary foci. Diagnostically, Alzheimer’s disease (AD) can be reduced to a simple formula: AD = symptoms + pathology, where pathology = amyloid plaques + neurofibrillary tangles (1). In symptomatic patients, plaques and tangles go hand in hand, but plaques are pathognomonic for AD, whereas tangles track better with symptom severity. So stating the formula in simplest terms: no amyloid plaques, no AD.

The FDA keyed in on this formula, based on advisory panel recommendations from 2008 and 2011, when it approved Lilly’s F18 florbetapir (Amyvid) on April 6, 2012; GE’s F18 flutemetamol (Vizamyl) on October 25, 2013; and Piramal’s F18 florteleban (Neuraceq) on March 19, 2014. For these radiopharmaceuticals, derived from molecular stains for amyloid plaques used at autopsy, and designed for the same purpose in vivo, the FDA quite reasonably required evidence that neuropathological determinations of AD based on imaging and autopsy agree.

The upshot? Three phase III efficacy trials reported by Lilly (2), GE (3), and Piramal (4) with nearly identical designs: recruit patients (n = 59, 67, and 82, respectively) with and without dementia who are going to die within a year or two, pre-mortem image and post-mortem autopsy their brains, and then compare the diagnosis of AD pathology independently derived from imaging and autopsy agree.

The FDA approved these tracers on the basis of those trials, along with a variety of post-marketing commitments, including calls to establish an academic registry to provide greater longitudinal follow-up data. With those commitments in hand, CMS will evaluate the tracers’ clinical value in the near future—a process that could take months or years. In the meantime, we look forward to more developments in this exciting area of research.

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AMYLOID PET: BOOM OR BUST?

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Continued on page 4. See Amyloid PET.
Biographical Sketches

**President**

Dr. Alexander Antoniou completed his undergraduate education at Tufts University with degrees in biology, biomedical engineering, and economics. Before starting at Tufts Medical School, he took a year off and completed a master's degree in economics (also at Tufts), which was financed by his excellent skills as a teaching assistant. Upon graduating from medical school, he moved south to complete a surgical internship in Gainesville (Go Gators!), only to realize how much he valued his weekends. He decided it was time for a change, and nuclear medicine greeted him with open arms. He found a home at Johns Hopkins as a nuclear medicine resident, which was a perfect position for someone like him—someone interested in being involved with patient care but not consumed by it, someone interested in research but not driven by it, someone interested in being involved with patient care and decision.

In his spare time Dr. Antoniou plays soccer, enjoys computer coding, and travels to warmer climates. He is also quadri-lingual (fluent in English, Greek, Arabic, and French) in addition to knowing the complex language of statistics in order to write research papers.

**Vice-President of External Affairs**

After receiving a B.S. in psychobiology from UCLA and an M.A. in psychology from Pepperdine University, Dr. Shana Elman ventured out of Southern California. She received her M.D. at the Medical College of Wisconsin in Milwaukee, taking 2 years off to complete a Doris Duke Clinical Research Fellowship at UT Southwestern in Dallas. This was followed by 2 years of general surgery residency at Virginia Mason Medical Center in Seattle, during which time she learned the impact of imaging on patient care and decided to switch to nuclear medicine. She has just completed her third and final year of nuclear medicine residency at the University of Washington and is currently completing a PET/CT Fellowship and a diagnostic radiology residency, also at the University of Washington.

Dr. Elman served as chief resident for 15 months and is currently serving as a member of her university’s GME Committee. She also sits on the ACR Practice Guidelines Committee for Nuclear Medicine, serves as the Nuclear Medicine Representative and Programs Chair of the Washington State Radiologic Society Resident-Fellow Section, and was one of the few residents chosen to participate in the Future Leaders Academy at the SNMMI mid-winter meeting. Dr. Elman looks forward to becoming more active in the Nuclear Medicine Residents Organization, in particular to ensure that the value and unique attributes of nuclear medicine training are not lost and to get involved in shaping and enhancing the educational model for nuclear medicine resident training, particularly as hybrid imaging modalities become more widely used.

In her spare time, Dr. Elman enjoys the outdoors...running, hiking, kayaking, skiing, and playing in the garden with her chickens.
Amyloid PET continued from page 1.

and autopsy, assuming autopsy to be the standard of truth. The companies' three studies were not designed for comparative effectiveness, of course, but I’m comfortable sticking my neck out on the hypothesis that Amyvid, Vizamyl, and Neuraceq are in the same ballpark of accuracy (93%, 88%, and 91%, respectively, for readers trained in person), with sensitivities and specificities > 80% (possible exception: Neuraceq might be a bit more sensitive and less specific relative to its peers). In addition, the companies each provided adequate evidence of reader reliability across training mediums and representative patient populations. OK, so amyloid radiotracers are ~90% accurate relative to amyloid stains at autopsy. The indications for the two must be the same, then, right? Here’s where the gray of life clashes with the black-and-white of death. The approved identical indication for Amyvid, Vizamyl, and Neuraceq is the following mouthful: “Amyvid/Vizamyl/Neuraceq is a radioactive agent for Positron Emission Tomography (PET) imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s Disease (AD) and other causes of cognitive decline. A negative scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient’s cognitive impairment is due to AD. A positive scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations. Limitations of use: a positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder.”

Remember: AD = symptoms + amyloid plaques, so the indication for amyloid staining in symptomatic patients at autopsy is simple: to diagnose AD. With amyloid radiotracers, then, why all the verbiage illogically implying that a negative scan reduces the post-test probability of AD, but a positive scan fails to raise it? The fundamental reason is a gap in knowledge that only decades of longitudinal imaging will address: the significance of amyloid plaques in asymptomatic individuals. In symptomatic individuals, however, a double standard applies to the interpretation of amyloid plaques demonstrated at autopsy (conclusion: patient had AD) versus at PET (conclusion: patient has “moderate to frequent amyloid neuritic plaques,” huh?). Until that double standard gets resolved (and payers revalue diagnosis), the cause of millions suffering from cognitive decline will likely remain needlessly unclear.

REFERENCES (available at amyloidpet.fotenos.com)

Figure Legend:
Midbrain axial slices from normal Amyvid, Vizamyl, and Neuraceq PET scans display intact gray/white differentiation. The three tracers are reported to have approximately equal accuracy in separate efficacy studies submitted to the FDA.

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of our long-term plans include developing a new education portal as a repository of information and resource for our residents, as well as becoming actively involved with the requirements of the new H.R. 4302, the Protecting Access to Medicare Act of 2014, signed by President Obama on April 1. More on the progress of these activities and how you can get involved will be available in the fall issue of the Scintillator. I wish all incoming residents a productive year in nuclear medicine, and I extend an invitation to join this community of residents for the betterment of our field.

Warmest regards,
Alexander Antoniou, MD, MA
NMRO President
**ACROSS**

1. Effect’s severity increases as dose increases; for example, cataracts.

5. The activity of 1 gram of radium, or $3.7 \times 10^{10}$ disintegrations per second.

6. Technetium’s daughter.

7. $^{14}\text{F}$ and $^{18}\text{F}$, for example (plural).

9. Whoops, I dropped 2 mCi of $^{131}\text{I}$ on the floor! (two words).

11. Invented the positron scintillation camera.

12. First president of ACNM.

13. $^{64}\text{Cu}$-ATSM can image this radiation resistance tumor property.

**DOWN**

2. First woman to win a Nobel Prize (two words).

3. Teratomatous tumor with functioning thyroid tissue (two words).

4. Does not require a transport index (two words).

8. Associated with gangrenous cholecystitis (two words).

10. Test to evaluate patient with vitamin B12 deficiency.

14. Chelator used with $^{111}\text{In}$–labeled leukocytes.
Interesting Correlative Case Report: Fibrous Dysplasia

Tatianie Jackson, MD

Case Report

A 26-year old woman presented to the emergency department with abdominal pain in the right lower quadrant. A contrast-enhanced CT scan of the abdomen and pelvis was obtained. This did not show any intraabdominal pathology to explain the patient's pain. However, there was an incidentally found heterogeneous lesion centered in the medullary space of the right femoral neck with relatively lucent and sclerotic architectural changes (Figure 1). Given this finding, the patient was prompted to see an orthopedic surgeon.

Approximately 4 months later she saw an orthopedic surgeon, who conducted a full physical exam and reviewed all correlative images. On the physical exam the physician noted a slight expansion in the mid to distal third of the tibia. The expansion was not painful to palpation, and there was no soft-tissue mass.

Radiography of the right lower extremity (Figure 2) showed a relatively well-circumscribed, heterogeneously dense, lobulated lesion with small septations in the right femoral neck that corresponded to the initial abnormality on the CT scan. In addition, there were multiple additional well-circumscribed lesions in the distal femur and throughout the tibia. To varying degrees, several of these also demonstrated thin sclerotic borders and serpiginous calcifications or septations, as well as some lytic and expansile features in the distal tibia. Some of the other lesions also appeared to have a ground-glass, hazy appearance in the internal matrix. Soon after the radiographs had been obtained, an MDP bone scan was obtained to evaluate the extent of fibrous dysplasia (Figure 3). This scan showed prominent intense radiotracer uptake in most (but not all) of this patient’s right-lower-extremity lesions, including those in the distal femur and tibia. Additionally, there were two more subtle foci of uptake in the femoral diaphysis and in the distal tibia, not easily appreciated (at least prospectively) on the plain radiographs of the same area. Also of note, there was no abnormal radiotracer uptake in the right femoral neck to correspond to the abnormality on CT and plain radiography of that region. Lastly, she underwent MRI of the lower extremities (Figure 4). This scan showed multiple well-circumscribed low-T1/high-T2 lobulated-appearing lesions in the same areas of the right lower extremity seen previously, including the femoral neck, femoral diaphysis, femoral condyle, and throughout the tibia. Several of the tibial lesions also appeared expansile, with either no or minimal cortical thinning.

The patient was diagnosed with fibrous dysplasia and was given a one-time intravenous dose of Zometa and oral bisphosphonate for 6 months. After the 6-month therapeutic management with Fosamax, the patient was reported to be pain-free, with stable findings on plain radiography.

Figure 1: CT of pelvis.

Figure 2: AP plain films of right hip (A), femur (B), and leg (C).


Answers

Across

1. deterministic
2. Marie Curie
3. stroma ovarii
4. white I
5. curie
6. ruthenium
7. isotopes
8. rim sign
9. major spill
10. Schilling
11. Anger (Hal Anger in 1957)
12. Maxfield (J.R. Maxfield, MD, FACNM)
13. hypoxia
14. oxine

Down

Discussion:
Although the CT scan (Figure 1) was negative overall and the patient's abdominal pain resolved without intervention, there was an incidental finding of mixed lytic/blastic architectural changes in the right femoral neck. By itself, the differential diagnosis for this finding is quite broad, including both benign and malignant entities. Examples of the former include bone cysts, nonossifying fibromas, fibroxanthomas, fibrous dysplasia, or giant cell tumor. Examples of the latter include metastatic cancer, osteosarcoma, and fibrosarcoma. Some preliminary adjustments can be made to this differential. The medullary location of this lesion may favor a giant cell tumor (as well as the other malignant lesions), but the patient's lack of pain or gait abnormalities make this possibility less likely. Furthermore, her bony lesion did not extend into the adjacent subarticular end of the affected bone, which is characteristic of giant cell tumor [1]. Benign fibroxanthomas and fibrous dysplasia are virtually indistinguishable on CT. However, the affected area on CT demonstrated increased thickness of the native cortex with endosteal scalloping, which is not characteristic of fibroxanthomas but does not exclude fibrous dysplasia [1, 2].
Fibrous dysplasia has known characteristic imaging findings that can be seen over several imaging modalities, assisting in the correct diagnosis: multiple areas of lucent lobulated lesions, some with internal septations and calcifications on plain films. MRI is a sensitive means of establishing lesion shape, lesion content, and the size of the affected region. It also provides complementary information when performed in conjunction with CT imaging [2]. Fibrous dysplasia demonstrates low T1 but high T2 signal, mainly because of the well-vascularized lesions that contain numerous spindle cells, scattered osteoblasts, and multiple trabeculae varying in size. These characteristics make this an active metabolic process, accounting for the T2 signal abnormality. Lastly, MDP bone scans can be used to evaluate the extent of disease but are typically not obtained for benign or equivocal bone lesions, as these entities can have variable uptake of the radiotracer [1-3]. In rare cases, bone scans are helpful when plain films have normal or equivocal findings [2]. A typical bone scan of patients with fibrous dysplasia exhibits markedly increased radioactivity on delayed images, which may represent a function of a rich vascular supply to the involved bone as well as some degree of bone remodeling (Figure 3) [4].

Conclusion
This case highlights distinct findings of fibrous dysplasia on CT, plain film radiographs, bone scans, and MRI. Combining various imaging modalities helps to diagnose fibrous dysplasia from similar bone lesions, distinguish the extent of the disease, and rule out associated complications.

References