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Bone Scans in Neurofibromatosis: Neurofibroma, Plexiform Neuroma and Neurofibrosarcoma

Richard T. Kloos, Vittoria Rufini, Milton D. Gross and Brahm Shapiro
Division of Nuclear Medicine, Department of Internal Medicine, University of Michigan, and Department of Veterans Affairs Medical Centers, Ann Arbor, Michigan

Neurofibromatosis type 1 or von Recklinghausen’s disease is one of the most common autosomal dominant genetic disorders. Between 29% and 77% of patients may suffer from a wide range of skeletal abnormalities and, thus, patients with neurofibromatosis frequently undergo skeletal scintigraphy, at which time the common peripheral nerve soft-tissue tumors that occur in this syndrome (neurofibromas, plexiform neuromas and neurofibrosarcomas) may be demonstrated. Methods: Single or multiphase 99mTc methylene diphosphonate (MDP) bone scans were performed in five patients with neurofibromatosis as part of their clinical evaluation. Results: We imaged neurofibromas in three patients, cutaneous neurofibromas in one patient and a plexiform neuroma in one patient. Conclusion: Single- or multiphasic bone scans may localize common soft-tissue tumors in neurofibromatosis.

Key Words: bone diseases; neurofibroma; neurofibrosarcoma; peripheral nerve neoplasms


Neurofibromatosis type 1 or von Recklinghausen’s disease (1-4) is one of the most common autosomal dominant disorders with a frequency rate of 1 in 3000 live births, an estimated prevalence of 30 patients per 200,000 population. This disease affects about 100,000 people in the United States with about 50% of cases representing new mutations (5-8). The gene responsible for its genesis has recently been mapped and cloned (9,10). Affected tissues include those of neuro-ectodermal, mesenchymal and endodermal origins. The phenotypic manifestations are protein and may vary from no more than six café-au-lait spots 15 mm in diameter (5 mm in prepubescent patients) to amongst the most grotesque deforming lesions encountered in clinical medicine (5-7). The diagnostic criteria are listed in Table 1. The syndrome of bilateral acoustic
TABLE 1
Diagnostic Criteria for von Recklinghausen’s Disease
(Neurofibromatosis Type 1)*

<table>
<thead>
<tr>
<th>Type</th>
<th>Genetic:</th>
<th>Cutaneous:</th>
<th>Ocular:</th>
<th>Skeletal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(a) Identification of the presence of the gene. (b) One or more first degree relatives meeting the clinical criteria for diagnosis of neurofibromatosis 1.</td>
<td>(a) Café-au-lait macules, 6 or more with greatest diameter over 15 mm (5 mm in prepubescent children). (b) Two or more neurofibromas of any type. (c) One or more plexiform neuromas. (d) Auxiliary or inguinal freckling.</td>
<td>(a) Optic glioma. (b) Two or more hamartomas of the iris (Lisch nodules).</td>
<td>(a) Distinctive sphenoid dysplasia. (b) Cortical thinning of long bones (with or without pseudarthrosis).</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Clinical diagnosis is made if a patient has positive proof of carrying the gene or manifests two or more of the clinical criteria [based on reference (11)].

neuromas (neurofibromatosis type 2) should not be confused with von Recklinghausen’s disease, as they are genetically distinct (5–7). There are rare cases of neurofibromatosis which share characteristics of both syndromes.

Von Recklinghausen’s disease is relatively common and 29%–77% of cases are associated with various with skeletal abnormalities (5,6,12–14) (Table 2). Consequently, patients with this disorder commonly are referred to nuclear medicine specialists for skeletal scintigraphy. In addition to the expected depiction of skeletal abnormalities (26), 99mTc methylene-diphosphonate is taken up on three phase and delayed bone scintigraphy by a variety of soft-tissue lesions in von Recklinghausen’s disease, including neurofibromas, plexiform neuromas and neurofibrosarcomas. Prior reports of such uptake have been sparse (27–29) and the phenomenon is listed are “rare” in a standard compendium of scintigraphic findings (30).

METHODS

Patients

Patient 1. A 34-yr-old man with neurofibromatosis, previous cosmetic facial surgery for disfiguring neurofibromas, right hand plexiform neuroma (Fig. 1) and thoracic kyphosis, developed an enlarging, painful, left forearm mass (17 cm). Fine needle aspiration (FNA) demonstrated neurofibrosarcoma. CT revealed significant soft tissue and bone destruction by the forearm mass. A 99mTc-MDP bone scan (Figs. 2, 3) excluded distant osseous metastatic disease in anticipation of an above-elbow amputation. Pre-operative MRI demonstrated a 6 cm paraspinal (C2–C5) mass confirmed by FNA to represent neurofibrosarcoma. Despite five cycles of palliative chemotherapy with adriamycin, ifosfamide, mesna and external beam radiation therapy to the paraspinal mass, the disease progressed. Taxol therapy was initiated and fever, chills and night sweats with progressive forearm mass ulceration were accompanied by a foul smelling discharge. Those symptoms were present at the scheduled admission for the second cycle of therapy. The patient refused an above the elbow amputation. A follow-up CT demonstrated paraspinal mass enlargement and spinal canal compression.

FIGURE 1. Plexiform neuroma radiographic features (Patient 1). Note the extensive lobulated soft tissue masses, abnormal atrophic metacarpals and phalanges affecting the 3rd, 4th and 5th rays of the right hand.

FIGURE 2. Technetium-99m-MDP three-phase bone scan (Patient 1). (A) Selected frames from the nuclear angiogram shows increased blood flow to plexiform neuroma of right hand and neurofibrosarcoma of left forearm (which has hyperemic rim and “cold” center) (arrows). (B) Marked increase in blood pool affecting the same regions.

TABLE 2
Typical Skeletal Lesions of von Recklinghausen’s Neurofibromatosis

<table>
<thead>
<tr>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoplasia of the walls of the orbit (11,13)</td>
</tr>
<tr>
<td>Calvarial defects: especially involving the parietal bones and left lambdoid suture (15–17)</td>
</tr>
<tr>
<td>Kyphoscoliosis (both idiopathic type and a short, sharp angulating type involving 4–6 vertebral segments with associated vertebral and rib abnormalities) (11,13,14,16,18)</td>
</tr>
<tr>
<td>Vertebral body erosion or scalloping (11,14,16,18)</td>
</tr>
<tr>
<td>Spinal and cranial nerve foramina erosion or enlargement (11,16,18)</td>
</tr>
<tr>
<td>Hypoplastic vertebral pedicles (19)</td>
</tr>
<tr>
<td>Thoracic and lumbar meningocoele (11,15,16)</td>
</tr>
<tr>
<td>Hip and pelvic deformities (11,12,20)</td>
</tr>
<tr>
<td>Costal scalloping, rib notching, and ribbon-like ribs (11,16,18,19)</td>
</tr>
<tr>
<td>Greater and lesser sphenoid wing abnormalities (11,15,16)</td>
</tr>
<tr>
<td>Macrocranium (11,21)</td>
</tr>
<tr>
<td>Zygomatich dysplasia (11)</td>
</tr>
<tr>
<td>Mandibular and maxillary deformity (11,13,15,22)</td>
</tr>
<tr>
<td>Long bone cortical dysplasia (18,21), metaphyseal and diaphyseal sclerosis (14), intramedullary linear sclerosis (23), subperiosteal hematomata (11,14,18), bowing (13,14,16,24), subperiosteal or cortical cyst lesions (11,13,14,21,24,25), pathological fracture (24), and pseudarthrosis (11,13,14,16,18)</td>
</tr>
<tr>
<td>Localized or hemi-hypophrophy (11,13,14)</td>
</tr>
<tr>
<td>Localized or hemi-hypertrophy (14,16,25)</td>
</tr>
</tbody>
</table>
invasion. Palliative measures were requested. Death soon thereafter was believed to result from diaphragmatic paralysis.

Patient 2. A 45-yr-old female was diagnosed with Charcot-Marie Tooth disease as a child and suffered progressive bilateral equinovarus deformity. This was treated with bilateral triple arthrodesis with a transfer of the anterior tibial tendons to the cuboid bones. She also had lifelong hand and lower extremity weakness, including bilateral foot drop, muscle atrophy and recurrent left patella dislocation. The female developed multiple neurofibromas at 16 yr of age and was diagnosed with neurofibromatosis at age 18 yr. She underwent multiple surgical resections of painful or disabling neurofibromas, including those from the ulnar nerves bilaterally, both hands, the right perilumbar area and the right forearm. There was long standing proptosis and exophthalmos. Right facial and trigeminal nerve neuromas caused right sided facial paralysis which led to multiple subsequent cosmetic and partial function restoring facial surgical procedures. Removal of a 7 cm by 10 cm right neck vagus nerve neurolemoma was complicated by right vocal cord paralysis. A three-phase $^{99}$mTc-MDP bone scan was obtained to rule out a left ankle stress fracture (Fig. 4).

Subsequent serial head and neck CT examinations demonstrated the progressive appearance of a mass involving the right petrous bone, bilateral acoustic neuromas, multiple expanding intracranial meningiomas, a high cervical mass within the cervical canal with spinal cord compression at C1 and C2, left orbital schwannomas and tracheal compression. The patient was rendered deaf, dysarthric, visually impaired and hyper-reflexic. The patient likewise had bilaterally impaired vocal cord function and was experiencing shortness of breath.

The patient underwent debulking of the cervical schwannoma with C1–C2 laminectomy and elective tracheostomy. Future surgical considerations include interventions aimed at the vocal cord dysfunction, the right trigeminal neuroma filling the ear and temporal bone, both acoustic neuromas and auditory brain stem implantation. The patient’s form of neurofibromatosis currently been considered a variant of type 2. No family members have neurofibromatosis the patient does not have café-au-lait spots or Lisch nodules. The bilateral acoustic neuromas and extensive meningiomas are consistent with neurofibromatosis type 2. Such patients may develop peripheral neurofibromas in the cervical region which are frequently large. Neurofibromas of the hands are also commonly observed. No definitive genetic studies are available regarding this patient.

Patient 3. A 29-yr-old man with a family history of neurofibromatosis, café-au-lait spots, status postresection of a medial left thigh plexiform neurofibroma 14 yr prior to evaluation and one other neurofibroma above the left eye was studied. Following resection, the residual lesion slowly increased in size until rapid growth associated with an increasingly hard and irregular consistency, increased lesion pigmentation and mild pain with activity began 10 mo prior to evaluation. CT demonstrated the mass to be centered medially in the soft tissues and inseparable from the adjacent adductors with overall dimensions of $20 \times 18 \times 15$ cm. Suspicion of right symphysis/inferior pubic ramus osseous metastatic disease prompted $^{99}$mTc-MDP bone scintigraphy (Fig. 5). Chest radiograph and CT demonstrated innu-
merable widespread, and diffuse pulmonary nodules varying in size from several millimeters up to 5 cm. A core needle biopsy of the thigh mass demonstrated a malignant peripheral nerve sheath tumor (spindle cell) in association with neurofibroma consistent with a neurofibrosarcoma.

**Patient 4.** A female infant was diagnosed with pulmonary valve stenosis at age 2 mo, > 20 café-au-lait spots noted at age 3 mo, axillary and inguinal freckling, neurofibromas and progressive kyphoscoliosis also beginning at age 3 mo. A thoracic, abdominal and pelvic CT scan at age 10 mo demonstrated a left paraspinal thoracic mass at the point of levoscopyosis with a density of 34 Hounsfield units. A cervical, thoracic and lumbosacral MRI study demonstrated the mass to be 6 × 3 × 2 cm in diameter with heterogeneous enhancement and penetration of at least one neural foramina. Operative resection of the thoracic mass revealed many plexiform extensions which could not be excised. The sympathetic chain was invaded by tumor and soft-tissue infiltrations. Tissue pathology diagnosed ganglioneuroma and ganglioneuroblastoma, and Shimada classification, including: stroma rich, nodular and intermediate differentiation (unfavorable histology). Surgery was complicated by left Horner's syndrome. Follow-up neck, chest, abdominal and pelvic CT demonstrated a low attenuation mass which encased the celiac axis, superior mesenteric artery and splayed the pancreas and splenic vein. Bone marrow aspirate and biopsy, 24 hr catecholamines, ferritin, and 131I- and [123I]MIBG scintigraphy studies showed no abnormalities. A 99mTc-MDP bone scan showed no osseous metastatic disease. Biopsy of the celiac mass demonstrated ganglioneuroma. Serial follow-up bone scans (Fig. 6), MIBG studies and CT scans have not shown evidence of local progression or metastatic disease. Orthopedic consultation documented rigid kyphoscoliosis and spinal bracing was instituted which she tolerated suboptimally. Despite careful follow-up, her curvatures progressed to 95° levoconvex thoracic kyphoscoliosis and 100° dextroconvex thoracolumbar scoliosis by 45 mo of age.

**Patient 5.** A 23-yr-old woman was diagnosed at age three with a presumptively new mutation causing neurofibromatosis based on > 6 café-au-lait spots and Lisch nodules, with the subsequent development of multiple neurofibromas by age 16 (which increased in number during two subsequent pregnancies and oral contraceptive use), and a neurofibromatosis affected child with unaffected parents. During a prenatal visit, a left

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**TABLE 3**

Radiopharmaceutical Uptake by Soft-Tissue Lesions in von Recklinghausen's Disease

<table>
<thead>
<tr>
<th>Radiochromaphetic</th>
<th>Findings</th>
<th>Significance</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>99mTc-diphosphonates</td>
<td>Uptake in neurofibromas, plexiform neuromas and neurofibrosarcomas.</td>
<td>Soft-tissue uptake noted in all types of lesions, perhaps more often in malignant tumors. Does not necessarily mean bone involvement.</td>
<td>Current report (28) and (27) are the same case, (29,30)</td>
</tr>
<tr>
<td>99mTc(V)DMSA</td>
<td>Photon deficient subperiosteal hemorrhage with uptake in elevated periosteum.</td>
<td>Tracer uptake occurs in both benign and malignant lesions. Avoid confusion with parotid gland tumors.</td>
<td>(35,36), (37–39)</td>
</tr>
<tr>
<td>99mTc]perchethenate</td>
<td>Uptake in neurofibroma and plexiform neurofibroma.</td>
<td>Scintigraphic uptake of 99mTc-DTPA is analogous to Gd-DTPA used in nuclear magnetic resonance imaging. Uptake occurs in other soft-tissue pathologies and may reflect overall active fibroblast uptake.</td>
<td>(32,33,40–43)</td>
</tr>
<tr>
<td>99mTc-DTPA</td>
<td>Uptake in neurofibromas, malignant schwannomas and plexiform neuromas.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>99mTc-sulfur colloid</td>
<td>Dilated lymphatics and enlarged lymph nodes in elephantiasis neuromatosa.</td>
<td>Abnormal lymphatic drainage depicted.</td>
<td>(44)</td>
</tr>
<tr>
<td>67Ga-citrate</td>
<td>Uptake in neurofibroma.</td>
<td>Gallium uptake may distinguish malignant from benign lesions.</td>
<td>(26,45)</td>
</tr>
<tr>
<td>131I</td>
<td>Uptake in abdominal neurolemoma.</td>
<td>Avoid false-positive diagnosis of functioning thyroid cancer metastasis.</td>
<td>(46)</td>
</tr>
<tr>
<td>123I or [131I]MIBG†</td>
<td>Uptake in pheochromocytomas but not in ordinary neurofibromas.</td>
<td>MIBG uptake helps to distinguish pheochromocytoma from most neurofibromas. MIBG uptake has been reported in atypical schwannoma.</td>
<td>Current report, (47,48)</td>
</tr>
<tr>
<td>[18F]FDG</td>
<td>Uptake greatest in malignant lesions.</td>
<td>Generally [18F]FDG uptake is greatest in malignant lesions.</td>
<td>(49)</td>
</tr>
<tr>
<td>197Hg-chlormerodrin</td>
<td>Uptake in plexiform neurofibroma.</td>
<td>Normal uptake occurs in the nasopharynx, superior sagittal sinus and parotid glands.</td>
<td>(39)</td>
</tr>
</tbody>
</table>

*The same would probably be true of 123I.
†The same would probably be true of 18F and radiobromine-labeled analogs.
lower quadrant abdominal mass was detected and subsequently characterized by CT and MRI as being $9 \times 8 \times 7$ cm in size and medial to the left iliac wing displacing the abdominal musculature. The mass was heterogeneous in density with central low attenuation necrosis, irregularly contrast enhancing and without associated satellite lesions or lymphadenopathy. In retrospect, a pricking, burning, itching intermittent pain was experienced for 2 yr above the left knee which radiated to the left groin. This pain was relieved by left hip flexion and worsened by hip extension. Examination revealed weakness of the left leg with decreased left knee reflex and impaired sensation in the distribution of the anterior femoral nerve. Needle aspiration cytology of the mass was nondiagnostic, while incisional wedge biopsy demonstrated a high grade neurofibrosarcoma arising within a benign neurofibroma. A $^{99m}$Tc-MDP bone scan was obtain to exclude osseous metastatic disease (Fig. 7). Chemotherapy and external beam radiation therapy were performed, and after partial tumor regression the patient underwent primary tumor resection without recurrence through 3.5 yr of follow-up observation.

**DISCUSSION**

Many of the neurogenic tumors in von Recklinghausen’s disease may show significant uptake of diphosphonate bone tracers. The increased vascularity and capillary permeability of the tumors in this study also resulted in some of the lesions showing tracer uptake on all three phases of the bone scan. In this respect, these lesions join the ever-growing group of tumors that manifest this phenomenon (which may or may not be associated with soft-tissue calcification either macroscopically or microscopically) (31). The sensitivity of scintigraphy with diphosphonate bone tracers to detect these soft-tissue tumors is not known (32,33).

A wide range of radiopharmaceuticals have been employed for various purposes to study the soft tissues tumors of von Recklinghausen’s neurofibromatosis (Table 3). In addition, the literature is extensive on the use of radioisotope bone scanning for acoustic neuromas which occur in neurofibromatosis type 2 and other central nervous system tumors which occur in both neurofibromatosis types 1 and 2 and which lie outside the scope of this study (15,50). The bone scan may be useful in the management of some of the skeletal abnormalities associated with neurofibromatosis (Table 2). This is particularly true for follow-up after surgical intervention (e.g., after surgical correction of scoliosis or in the evaluation of the healing of cortical defects following repair (perhaps including the placement for bone grafts).

It has been reported that sarcomatous change in neurofibromatosis occurs in 2%–16.5% of patients (11,16,51). In attempting to distinguish between benign neurofibroma or plexiform neurofibroma and neurofibrosarcoma, gallium or $^{18}$F-FDG avidity suggests malignancy (45,49).

Pheochromocytoma occurs in 1%–4% of patients with neurofibromatosis type 1 (47). The distinction of pheochromocytomas and closely related neuroendocrine tumors from neurofibromas has posed a major challenge for anatomical imaging modalities. Iodine-131- or $^{123}$I-metaiodobenzylguanidine (MIBG), however, has proven efficacious in this task as neurofibromas ordinary are not MIBG-avid. The same would probably be true for related radiopharmaceuticals (e.g., $^{11}$C-hydroxyephedrine and radio-Br or F-labeled analogs of MIBG). There are rare reports of MIBG uptake by atypical schwannomas (48). The role of radiolabeled somatostatin analogs (e.g., $^{11}$In-octreoscan) in distinguishing pheochromocytomas from neurofibromas is similar to that of MIBG.

**CONCLUSION**

Scintigraphic techniques have a significant role to play in the investigation of skeletal abnormalities and soft-tissue tumors in von Recklinghausen’s neurofibromatosis. All three of the common peripheral nerve soft-tissue tumors that occur in this syndrome may show uptake of $^{99m}$Tc-labeled bone-seeking radiopharmaceuticals on three-phase or delayed bone scintigraphy.

**ACKNOWLEDGMENTS**

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**REFERENCES**


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Quantitative Comparison of Planar and SPECT Normal Data Files of Thallium-201, Technetium-99m-Sestamibi, Technetium-99m-Tetrofosmin and Technetium-99m-Furifosmin

Hitoshi Naruse, Edouard Daher, Albert Sinusas, Diwakar Jain, Donna Natale, Jennifer Matterà, Robert Makuch and Frans J.Th. Wackers
The Cardiovascular Nuclear Imaging Laboratory, Departments of Diagnostic Radiology, Medicine, Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut

In recent years, several of 99mTc-labeled myocardial perfusion imaging agents have been developed, such as 99mTc-sestamibi, 99mTc-tetrofosmin and 99mTc-furifosmin. Although images obtained with these new tracers have a general similar appearance, there are differences in the myocardial kinetics, body distribution, general quality of images and imaging protocols. The aim of this study was to quantitatively compare normal exercise planar and SPECT datafiles obtained with 201TI and 99mTc-labeled agents. Methods: Lower-limit-of-normal curves were generated for each specific radiopharmaceutical from normal subjects with low (<3%) pretest likelihood of coronary artery disease using circumferential count distribution profiles from planar and SPECT exercise images. Lower-limit-of-normal curves were statistically compared using the nonparametric Kruskall-Wallis and Wilcoxon tests. Results: Planar and SPECT lower-limit-of-normal curves generated for each radiopharmaceutical showed general similarities. Statistically significant differences have been developed such as 99mTc-tetrofosmin (3) and 99mTc-furifosmin (4). These new radiopharmaceuticals provide improved image quality, particularly when used for SPECT. Normal images with each of the above imaging agents, using either planar or SPECT imaging, have visually a similar general appearance i.e., more or less homogeneous myocardial uptake. Nevertheless, there are marked differences in myocardial kinetics, body distribution, general quality of images and imaging protocols (2,3,5–7).

Quantification of planar and SPECT images enhances confidence and reproducibility of image interpretation (8–10). In addition, quantitative measurement of myocardial perfusion abnormalities has shown to be of importance for prognostic risk stratification in individual patients (11–13). The most important components of image quantification are graphic or color-coded display of relative myocardial radiopharmaceutical distribution and normal data files for comparison with patient image data (9,14).

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Key Words: normal data files; quantification; thallium-201; sestamibi; tetrofosmin; furifosmin.


Several new radiopharmaceuticals have been introduced in recent years for stress myocardial perfusion imaging. Because of unfavorable characteristics of the conventional imaging agent, 201TI (1), 99mTc-labeled agents with better imaging properties have been developed such as 99mTc-sestamibi (2), 99mTc-tetrofosmin (3) and 99mTc-furifosmin (4). These new radiopharmaceuticals provide improved image quality, particularly when used for SPECT. Normal images with each of the above imaging agents, using either planar or SPECT imaging, have visually a similar general appearance i.e., more or less homogeneous myocardial uptake. Nevertheless, there are marked differences in myocardial kinetics, body distribution, general quality of images and imaging protocols (2,3,5–7).

Quantification of planar and SPECT images enhances confidence and reproducibility of image interpretation (8–10). In addition, quantitative measurement of myocardial perfusion abnormalities has shown to be of importance for prognostic risk stratification in individual patients (11–13). The most important components of image quantification are graphic or color-coded display of relative myocardial radiopharmaceutical distribution and normal data files for comparison with patient image data (9,14).