Different Uptake Patterns of Tc-99m MDP on Three Phase Bone Scan in a Neurofibromatosis Type I Patient with Multiple Neurofibromas and Neurofibrosarcoma: Case Report

Multipl Nörofibrom ve Nörofibrosarkom Olan Tip 1 Nörofibromatozisli Hastada Üç Fazlı Kemik Sintigrafisinde Tc-99m MDP'nin Farklı Tutulum Paternleri

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ABSTRACT We report a case of Neurofibromatosis Type I (NF-1) patient who had a palpable mass on the left inguinal and right popliteal region and multiple neurofibromas extending from the cervical region to the lumbosacral level demonstrated by magnetic resonance imaging (MRI). Three phase bone scan performed for evaluation of possible malignant transformation showed different uptake patterns in different lesions of the patient. Hyperemia and increased radiopharmaceutical uptake was seen in the left inguinal soft tissue (neurofibrosarcoma). Popliteal lesion (neurofibroma) could not be visualised on both blood pool and late static images. The lesion on the lumbosacral region was not apparent in blood pool phase but photopenic on late phase. Histopathological confirmation was not possible for this lesion due to high risk of complications. As a conclusion, in neurofibromatosis, increased uptake in blood pool phase should be a warning for malignant transformation independant of radiopharmaceutical uptake in the late phase.

Key Words: Neurofibromatosis 1; radionuclide imaging; soft tissue neoplasms

ÖZET Bu çalışmada sol inguinal, sağ popliteal bölge ve manyetik rezonans görüntüleme (MRG) ile tanımlanan servikal bölgeden lumbosakral bölgeye uzanan multipl nörofibromlar olan bir Nörofibromatozis Tip 1 (NF-1) vakası sunulmuştur. Olası malign transformasyon değerlendirilmesi için yapılan üç fazlı kemik sintigrafisinde hastanın farklı lezyonlarında farklı tutulum paternleri gözlendi. Sol inguinal yumuşak doku tümöründe (nörofibrosarkom) hiperemi ve artmış radyofarmasötik tutulumu izlendi. Popliteal lezyon (nörofibrom) hem kan havuzu fazında, hem de geç statik görüntüde izlenmedi. Lumbosakral bölgedeki lezyon kan havuzu fazında belirgin değildi, ancak geç fazda fotopenik idi. Olası komplikasyon riski yüksek olması nedeniyle histopatolojik konfirmasyon yapılamadı. Sonuç olarak, nörofibromatozisde, geç fazda radyofarmasötik tutulumundan bağımsız olarak kan havuzu fazında artmış tutulum, malign transformasyon için uyarıcı olabilir.

Anahtar Kelimeler: Nörofibromatozis 1; radyonuklit görüntüleme; yumuşak doku neoplazileri

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Neurofibromatosis Type I (Von Recklinghausen's Disease) is one of the most common genetic disorders seen 1 in 3000 live births. It is a single gene disorder with autosomal dominant trait but up to 50% of the cases arise due to spontaneous mutation.[1] Clinical presentation and prognosis is quite different in every case due to variable expression of the neurofibrin I (NF I gene).[2,3] It affects neuro-ectodermal, mesenchymal and endodermal originated tissues. The 7 clinical criteria used to diagnose NF1 are: Six or more café-au-lait spots or hyperpigmented macules greater

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than or equal to 5 mm in diameter in prepubertal children and 15 mm postpubertal age, axillary or inguinal freckles (>2), two or more typical neurofibromas or one plexiform neurofibroma, optic nerve glioma, two or more iris hamartomas (Lisch nodules), sphenoid dysplasia or typical long-bone abnormalities such as pseudarthrosis, existence of a first-degree relative (eg, mother, father, sister, brother) with NF1.[4] Cancer can arise from malignant peripheral nerve sheath tumor resulting from malignant degeneration of a plexiform neurofibroma. Malignant nerve sheath tumor was reported as the main cause of death (60%) in patients with NF-1 and excess mortality in NF-1 patients compared to the general population.[5,6] Risk factors for malignant transformation of neurofibromas have been reported as: deletion of the whole NF 1 gene, existence of neurofibromatous neuropathy, previous radiotherapy, history of malignant peripheral nerve sheeth tumor in a relative with NF Type I.[7-10] The diagnosis of malignant peripheral nerve sheeth tumors is challenging because they are generally deep located.[11] The clinical presentation of malignant transformation is characterized by serious and persistent pain, rapid increase in size of a neurofibroma, hardening in the nature of the tumor, new onset of neurological deficits.[12] These signs are actually nonspecific and neurofibromatosis patients already suffer from similar symptoms. Certain diagnosis of malignancy can only be made by surgical excision and histopathology. Magnetic resonance imaging can show the location and extent of the tumor and whole body MRI has been reported to estimate tumor burden but it is not reliable enough to differentiate malignant transformation.[12,13] Fluoro-18 fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) has been reported to be a sensitive and a specific tool in diagnosis of NF-1 associated tumors but maximum standardized uptake value (SUVmax) was not successful enough to predict tumor grade.[14,15] Technetium 99m-methylenediphosphonate (Tc-99m MDP) bone scan has been used to detect skeletal abnormalities in NF-1 patients but Tc-99m MDP was also reported to be taken up by soft-tissue lesions in NF-1.[16] Although late phase Tc-99m MDP uptake is not specific for sarcomatous change in neurofibromas, the role of three phase bone scintigraphy in determining malignancy is still unclear. Neurofibrosarcoma development is rare in NF-1 patients and malignant changes generally occur in deep seated tumors in childhood. We report an interesting case of a NF-1 adult with neurofibrosarcoma originating from the nerve sheeth of the femoral nerve in the inguinal region which was diagnosed by three phase bone scan.

CASE REPORT

42 years old male patient with NF Type I was referred to Nuclear Medicine Department for bone scan. The disease was first presented with cafe au lait spots and a left inguinal mass. Surgical excision of this mass revealed that it was a plexiform neurofibroma. Genetic analysis confirmed NF 1 gene mutation. He had undergone a total of 10 operations for cervical and thoracal neurofibromas originating from neural sheeth and left hand schwannoma in 10 years time. In the follow up, he came up with pain in both upper and lower extremities together with left inguinal and right popliteal palpable masses. Cervical-thoracal-lumbal MRI showed multipl mass lesions visulised hyperintense in T2 weighed images. The lesions were located in the extraforaminal region and started from the cervical level, extended to the lumbosacral level in columna vertebralis. Paratracheal, paraaortic and subpleural regions were also involved (Figures 1a and 1b). Although the MRI findings were compatible with multiple neurofibromas, bone scan was ordered in order to evaluate possible malignant transformation. Different uptake patterns in different regions were observed. On whole body blood pool imaging, there was marked hyperemia in the left inguinal region. Although thoracal region couldn't be interpreted easily due to the mediastinal blood pool activity, no other pathologically hyper or oligemic areas were observed in posterior position (Figure 2a). On late phase whole body scan, Tc-99m MDP uptake still existed on the left inguinal mass. There was no pathological uptake in the right popliteal region.

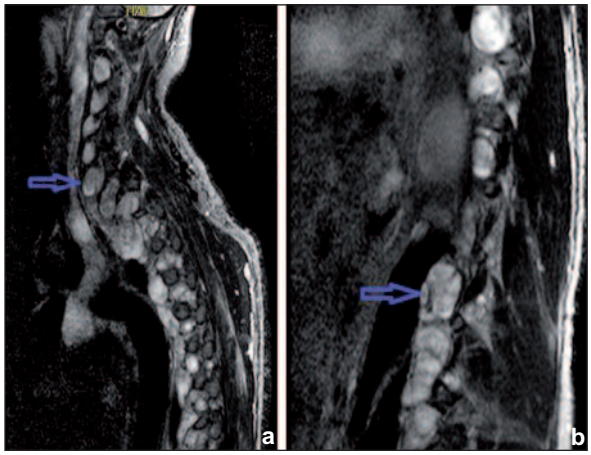
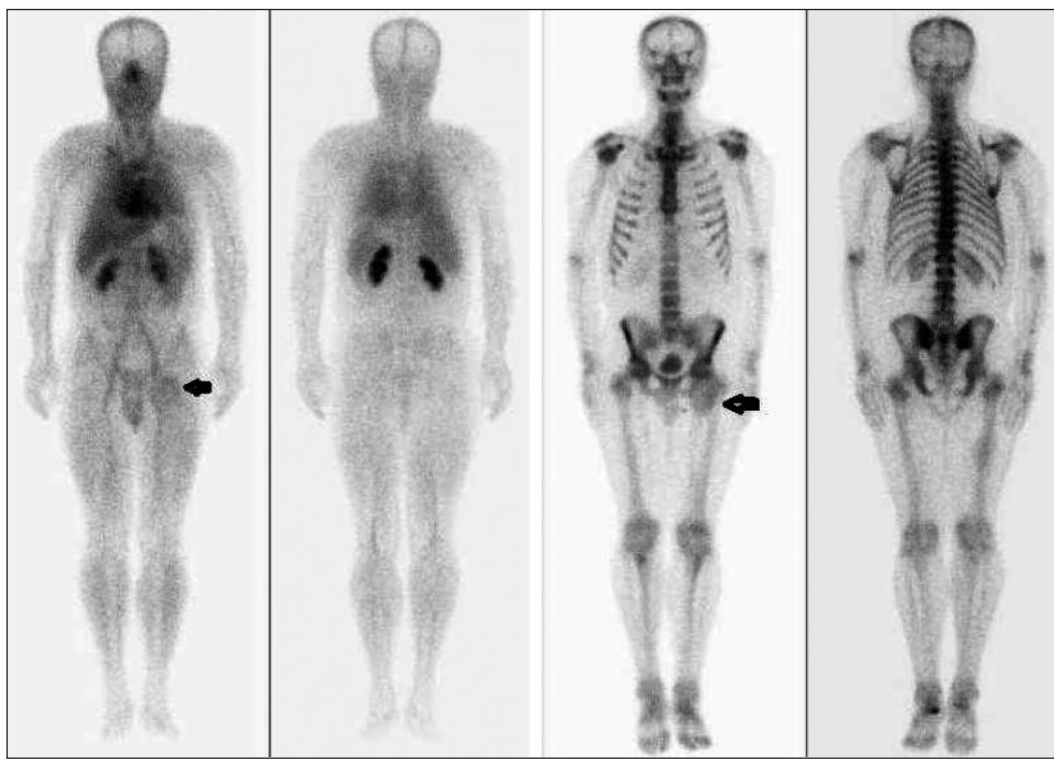


FIGURE 1: 1a and **1b:** Neurofibromas showing diffuse hyperintense thickening in nerve roots and extending from intraforaminal level to extraforaminal region demonstrated at short tau inversion recovery (STIR) sequences in sagittal plane on cervical-thoracal-lumber MRI examination.

Radiopharmaceutical distribution was quite homogenous throughout the columna vertebralis except for the photopenic area in the lumbosacral region (Figure 2b). The patient underwent surgery for the excision of some of his lesions. The left inguinal mass of 10x6x7 cm was histopathologically proven to be a neurofibrosarcoma. The right popliteal mass in dimensions 8,5x5,5x4,5 cm was a neurofibroma. Surgical excision and histopathological evaluation of the lumbosacral mass was not possible due to high complication risks.

DISCUSSION

Neurofibromatosis Type I (Von Recklinghausen's Disease) is a relatively common genetic disorder with autosomal dominant inheritance.[1] One of the most serious aspects of neurofibromatosis is development of cancer. Overall, patients with NF1 were 1.2 times more likely than expected to have a malignant neoplasm. Together with tumors of the central nervous system; which include astrocytomas, ependymomas, meningiomas, and some neuroectodermal tumors, leukemia, pheochroma-



2a 2b

FIGURE 2: 2a and **2b:** Whole body blood pool and late phase bone scan images. Hyperemia and increased Tc-99m MDP uptake was seen in the left inguinal soft tissue and excision of this mass revealed that it was a neurofibrosarcoma. Popliteal lesion could not be visualised on both blood pool and late static images which was then histopathologically proven to be a neurofibroma. Lumbosacral region was not apparent in blood pool phase but photopenic on late phase. Histopathological evaluation of the lumbosacral mass was not possible due to high complication risks. Activity uptake was quite homogenous on the rest of columna vertebralis.

cytoma; neurofibrosarcoma, fibrosarcoma, malignant schwannoma have been reported as secondary cancers in neurofibromatosis patients.[17-19] Malignant peripheral nerve sheeth tumors is one of the most frequent causes of death in NF1. They generally arise from benign neuromas and late diagnosis of malignant degeneration is associated with bad prognosis.[20,21] Malignant transformation of neurofibromas is hard to notice in the course of the disease because they don't have a specific symptom or clinical feature and sarcomas are generally located deep in the body embedded in other nonmalignant neurofibroma masses, unlike benign cutaneous neurofibromas.[11,12] Certain diagnosis of malignancy can only be made histopathologically. The standard imaging tool is currently MRI, but it has a limited sensitivity and specificity in detection of sarcomatous changes.[12,13] 18F-FDG PET/CT is now popular in soft tissue tumors. Its' sensitivity has been reported to be higher than whole body MRI in detecting malignant peripheral nerve sheeth tumors.[15] It is known that malignant peripheral nerve sheath tumors have a low metabolic rate and they generally show lower levels of SUVmax values. In a recent study, FDG avid malignant nerve sheeth tumors had a median SUVmax value of 2.2 and high metabolic activity (SUVmax>2.5) was correlated with tumor location: deep located tumors close to the trunk had higher levels of 18F-FDG uptake versus a relatively lower uptake in the tumors originated from peripheral nerves.[22]

Tc-99m MDP bone scan is performed in order to investigate coexisting skeletal disorders in NF-1. Tc-99m MDP was also reported to be taken up by soft-tissue lesions in NF-1.[16] The diagnostic use for differentiation of sarcomatous changes is controversial, as there are previous studies reporting Tc-99m MDP uptake in both three phases in soft tissue in neurofibromas, plexiform neuromas and neurofibrosarcomas.[23-25] We report bone scintigraphy findings of an adult NF-1 patient with neurofibrosarcoma unexpectedly located on femoral nerve instead of a truncal location. His first neurofibroma diagnosis was made by excision of a left inguinal tumor ten years ago and he recently had a recurrent mass originating from the same peripheral nerve. He also had a similar painful lump in the right popliteal fossa. Bone scan findings revealed hyperemia in the location of the neruofibrosarcoma but no oligemia or hypermia was detected anywhere else in the body. Tc-99m MDP uptake was apparent in the soft tissue in the left inguinal region in the late phase whole body scan but no other pathologically increased uptake could be detected in the soft tissues in the bone phase. However there was a focal photopenic area in the lumbosacral region. MRI showed that there were multiple lesions starting from the cervical region and extending to the sacrum. So the photopenic defect was probably due to one of these masses. Because surgery was not possible in this area, we don't know if the nature of this lumbosacral mass was benign or malignant.

In malignant or metastatic tumors, the role of three phase bone scan is controversial. Blood flow increase and hyperemia is frequently seen in these cases and blood flow increase is of diagnostic value in differentiation of malignity on bone scintigraphy.[26] In some cases, blood flow increase and hyperemia can be the only warning sign on bone scan and even no significant osteoblastic activity retention may be detected on late phase bone scan.[27] Our case was also an example for showing the value of blood flow increase and hyperemia in differentiating malignancy.

Many uptake patterns can be visualised on bone scan in soft tissue tumors in Neurofibromatosis Type I. Malignant transformation in benign neurofibromas is hard to detect. Increased uptake in blood pool phase should be a warning for malignant transformation independant of Tc-99m MDP uptake in the late bone phase and the localisation of the tumor in NF I patients.

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