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Neurofibromatosis Type 1-Associated Multiple Malignant Peripheral Nerve Sheet Tumors: A Case Report and Literature Review

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Abstract

Background: Neurofibromatosis type 1 (NF-1) is a genetic disorder characterized by café-au-lait macules, freckling, Lisch nodules, and neurofibromas. NF-1 patients have a special predisposition to tumorigenesis due to genetic mutations, affecting the tumor regulator systems. Malignant Peripheral Nerve Sheet Tumor (MPNST) is a highly aggressive soft tissue tumor that is usually associated with NF-1.

Case presentation: A 32-year-old woman was presented complaining of weakness, severe fatigue, weight loss, peripheral paresthesia, progressive generalized myalgia, bone pain, and a mass sensation in her right thigh since three months ago. She was a known case of NF-1 since childhood. After clinical and radiological evaluation, multiple masses were detected in the retroperitoneal cavity adjacent to the left kidney, uterus, and right thigh. Finally, the patient was planned for surgical excision of two masses with subsequent chemotherapy. Both excised masses were confirmed as MPNSTs by histopathological examination.

Conclusion: Regarding the predisposition of NF-1 patients to tumorigenesis and the high prevalence of peripheral nerve tumors among these patients, any masses changing their character should raise suspicion for malignancy. One of the serious malignant lesions is MPNST. The primary treatment plan for these malignant lesions is surgical excision with subsequent chemotherapy or radiotherapy based on individual characteristics.

Keywords: Case report, Malignant peripheral nerve sheet tumor, Neurofibromatosis 1, Peripheral nervous system neoplasms

1. Background

Neurofibromatosis type 1 (NF-1) is an autosomal dominant genetic disorder caused by NF-1 gene mutation. The gene encodes a protein called Neurofibromin. Loss of Neurofibromin or reduced function of the protein leads to RAS proto-oncogene activation and results in various clinical manifestations and predisposition to tumorigenesis (1, 2). Approximately, half of the NF-1 patients inherit a mutation while half of them have de novo mutations (3, 4).

Prominent clinical manifestations are café-au-lait macules, axillary and inguinal freckling, Lisch nodules (iris hamartoma), and neurofibromas (3, 5). Other findings include osseous dysplasia, hypertension, optic pathway glioma (OPG), central and peripheral nervous system involvement, and various benign or malignant tumors (2, 4). Peripheral nerve tumors are a group of rare tumors among the general population, including benign and malignant lesions. Neurofibroma, as a benign tumor, is commonly observed in association with NF-1. Malignant Peripheral Nerve Sheet Tumor (MPNST), also known as neurofibrosarcoma, is a highly aggressive soft tissue tumor that is often associated with NF-1 or radiation. Most NF-1-related MPNSTs originate from pre-existing plexiform neurofibromas (6, 7).

NF-1 diagnosis is based on clinical manifestations and according to the diagnostic criteria, the patient must have at least two of the following features: six or more café-au-lait macules, two or more neurofibromas of any type or one or more plexiform neurofibroma, axillary or inguinal freckling, optic glioma, two or more Lisch nodules, a distinctive bony lesion, and a first-degree relative with NF-1 (8).

Patient management is multidisciplinary due to the wide range of complications involving the eyes, nervous system, cardiovascular system, and bony skeleton. Surgical resection is a treatment of choice for most NF-1-associated tumors, including MPNSTs, although it is usually challenging regarding the tumor location and extension. Chemotherapy and radiotherapy are other treatment options; however, the superiority should be evaluated due to the risk of toxicity and secondary malignancies. Novel drugs acting by the suppression of tumorigenesis mechanisms have been developed with promising results (1, 3). Here, we report a case of NF-1 with multiple masses and two confirmed MPNSTs.

2. Case Presentation

A 32-year-old woman presented to the clinic complaining of headache, intermittent palpitation,

weakness, severe fatigue, anorexia, and weight loss since three months ago. Moreover, she had a history of Iron deficiency anemia. She was a known case of NF-1 since childhood. Going through the details of her symptoms during the patient interview, she complained of intermittent epigastric pain, a sense of pressure in the abdomen, as well as frequent nausea and vomiting (without relation to eating); however, she had normal defecation. In addition, she complained of peripheral paresthesia, progressive generalized myalgia, and bone pain. She said that there is an enlarging mass with severe pain in the posterior side of her right thigh preventing her from normal walking. She did not complain of any visual or hearing problems. She did not have a history of seizures, and her menstrual periods were regular. All of her symptoms began during the last three months and were exacerbated.

The patient was single. Her past medical history was considerable for NF-1 diagnosed based on cutaneous manifestations when she was three years old. The cutaneous manifestations including café-au-lait macules, axillary and inguinal freckling, and cutaneous neurofibromas were exacerbated from the age of 20 years. She did not have a history of premature or delayed puberty. Family history was negative for neurofibromatosis or any similar symptoms in first-degree relatives. She did not use any drugs; moreover, her allergy history and habitual history were unremarkable.

On the general physical examination, the patient was pale and cachectic, and her body mass index was 23.2 kg/m^2 (weight: 71 kg and height: 175 cm). She seemed older than her chronological age, and she had a depressed mood. The vital signs were as follows: Blood Pressure: 105/80 mmHg, Pulse Rate: 106/min, Respiratory Rate: 14/min, and O_2 Saturation: 94% (without O_2 support). She never had a fever during the disease course, and her systolic blood pressure never raised over 110 mmHg. There were diffuse café-au-lait macules, axillary and inguinal freckling, and cutaneous neurofibromas on her skin (Figure 1). The thyroid, breast, and lymph node examinations were normal. Furthermore, no pathological points were detected during the cardiac and pulmonary examinations. On the abdominal examination, there was mild epigastric tenderness without organomegaly or other pathological signs. There was diffuse tenderness on palpating most of the bones. The patient had severe proximal muscle weakness, especially in the pelvic girdle, and a positive Gower's sign. Additionally, she had bowed legs, kyphosis, and scoliosis. A round mass (estimated size: 10*17 cm) was palpated on the posterior aspect of the right thigh. It was firm, non-mobile, and tender on deep palpation. No other mass was palpated in limbs and fingers. The complete neurologic examination was performed, and it was normal, except for decreased muscle power (3/5) in the proximal muscle groups of extremities. Deep tendon reflexes were also normal.

Specific cardiovascular and ophthalmologic evaluations were done by the specialists. Ophthalmologic examination revealed Lisch nodules (also known as iris hamartoma) in both eyes without other pathological signs. The cardiovascular examination and echocardiographic evaluation in terms of pulmonic stenosis, mitral valve anomalies, and septal defects were normal.

Considering laboratory findings, the patient had anemia and markedly elevated Erythrocyte Sedimentation Rate (ESR). More details of laboratory findings are mentioned in Table 1. As the initial investigations, a Chest X-Ray (CXR) and abdominal ultrasonography were performed. CXR was normal, and the ultrasound examination of the abdomen showed a well-defined mass (5*4*3 cm) adjacent to the left kidney. Regarding the patient's gastrointestinal symptoms, an upper gastrointestinal (GI) endoscopy was performed and showed a hiatal hernia with Caremon ulcer. It was otherwise normal. The Bone Mineral Density test did not show any signs of osteoporosis or osteopenia.

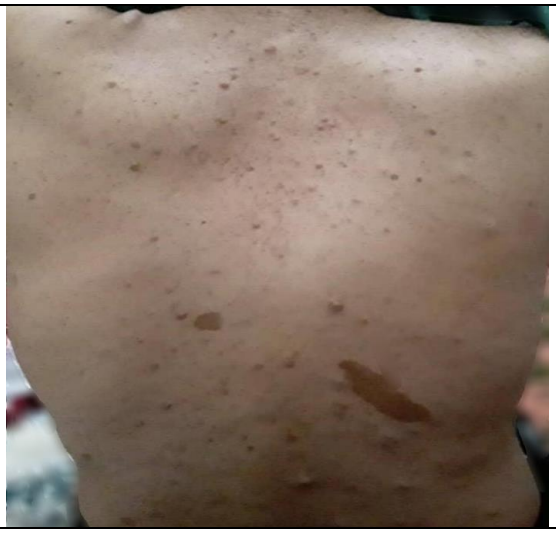

Figure 1. Cutaneous Manifestations

Table 1. Laboratory Data

Parameter	Level	Normal range
Complete Blood Count		
WBC (per µl)	10100	4000-12000
PLT (per µl)	390000	150000-450000
HB (g/dl)	10.1	12-16
MCV (fl)	75.2	75-100
MCH (pg)	22.7	25-34
MCHC (g/dl)	30.1	31-36
Iron Profile		
Serum Iron (µg/dl)	35	50-150
Ferritin (µg/L)	148	300-360
TIBC (µg/dl)	265	5-200
Electrolytes		
Sodium (mmol/L)	141	135-145
Potassium (mmol/L)	4.4	3.4-4.8
Calcium (mg/dl)	9.1	8.9-10
Magnesium (mg/dl)	1.9	1.7-2.2
Phosphorus (mg/dl)	3.8	2.8-4.5
Coagulation Profile		
PT (seconds)	11.7	11-13.5
PTT (seconds)	28.2	25-35
INR	0.9	Up to 1.1
Biochemistry		
BUN (mg/dl)	20	5-23
Creatinine (mg/dl)	0.7	0.4-1.3
AST (U/L)	21	3-45
ALT (U/L)	29	0-45
ALKP (U/L)	607	70-380
LDH (U/L)	354	140-280
ACTH (pg/ml)	24	10-60
Cortisol (µg/dl)	12.8	10-20
Vitamin B12 (pg/ml)	225	160-950
Vitamin D3 (ng/ml)	26.7	20-40
Thyroid Function		
TSH (mIU/L)	2	0.5-5
Inflammatory Markers		
ESR (mm/h)	126	1-15
CRP (qualitative)	+	Negative
24-hour Urine Collection		
Metanephrine (µg/day)	90	<350
Normetanephrine (µg/day)	287	<600

WBC: White Blood Cells, **PLT**: Platelets, **HB**: Hemoglobin, **MCV**: Mean Corpuscular Volume, **MCH**: Mean Corpuscular Hemoglobin, **MCHC**: Mean Corpuscular Hemoglobin Concentration, **TIBC**: Total Iron Binding Capacity, **PT**: Prothrombin Time, **PTT**: Partial Thromboplastin Time, **INR**: International normalized ratio, **BUN**: Blood Urea Nitrogen, **AST**: Aspartate Aminotransferase, **ALT**: Alanine Transaminase, **ALKP**: Alkaline Phosphatase, **LDH**: Lactate Dehydrogenase, **ACTH**: Adrenocorticotropic Hormone, **Vitamin D3**: 25-Hydroxy Vitamin D3, **TSH**: Thyroid Stimulating Hormone, **ESR**: Erythrocyte Sedimentation Rate, **CRP**: C - reactive protein

Looking for possible masses across the body, the patient underwent brain, cervical, thoracic spine, abdominal, and pelvic magnetic resonance imaging (MRI) in one day. Brain MRI (with and without intravenous contrast) revealed a few T2 hyperintense lesions in the white matter with the greatest dimension of 8*4 mm in the left aspect of the corpus callosum body (some of them were enhanced) suggestive of NF-associated bright spots. Bilateral optic nerve enlargement was seen without an obvious mass lesion. Cervical MRI (with and without intravenous contrast) showed a T2 hyper-signal lesion (16*3 mm) in the spinal cord at C1 level suggestive of NF-associated bright spots or demyelinating lesion. Severe kyphosis, multi-level disc dehydration, disc osteophyte complex, and a few enhancing cutaneous nodules were also detected. The thoracic spine MRI (with and without intravenous contrast) was normal, except for right-sided scoliosis, multi-level disc degeneration, and several enhancing cutaneous nodules. In the abdominal MRI (with and without intravenous contrast), a well-defined mass lesion (54*42*35 mm) was detected adjacent to the anterior-inferior aspect of the left kidney that has T1 iso-signality and T2 hyper-signality with heterogeneous enhancement suggestive of neurofibroma or paraganglioma (Figure 2). The pelvic MRI (without intravenous contrast) revealed an enlarged uterus with multiple myomas (greatest dimension: 90*60 mm) and a large heterogeneous mass lesion (160*90 mm) in the posterior soft tissue of the right thigh. Furthermore, a few enhancing cutaneous nodules were noted (Figure 3). Biopsy of the thigh lesion was recommended by the radiologist for further evaluation; accordingly, a core needle biopsy was performed, and histopathological examination of the specimen showed malignant mesenchymal tumor score 4, grade 2/3 based on

FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer) grading system compatible with malignant peripheral nerve sheet tumor (low grade).

Finally, the patient was diagnosed as NF-1 with multiple masses. She was planned to have surgery for the excision of the retroperitoneal mass in the abdomen adjacent to the left kidney and the mass lesion in the right thigh. A retroperitoneal mass lesion (6*4.5*4) cm was excised, and its histopathological evaluation revealed spindle cell sarcoma suggestive of Malignant Peripheral Nerve Sheet Tumor (MPNST) grade 3 based on FNCLCC system. A capsulated 17.5*10*7.5 cm mass was excised from the thigh soft tissue, and its histopathological evaluation again showed spindle cell sarcoma with extensive necrosis suggestive of MPNST grade 3 based on the FNCLCC grading system (Figure 4).

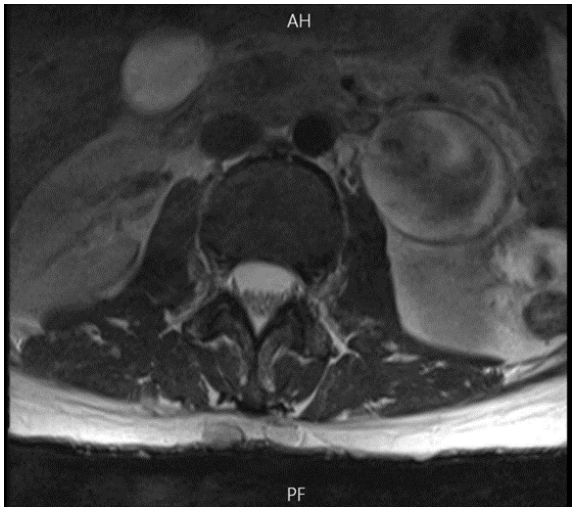

Figure 2. Abdominal MRI, T2, Axial, Retroperitoneal mass

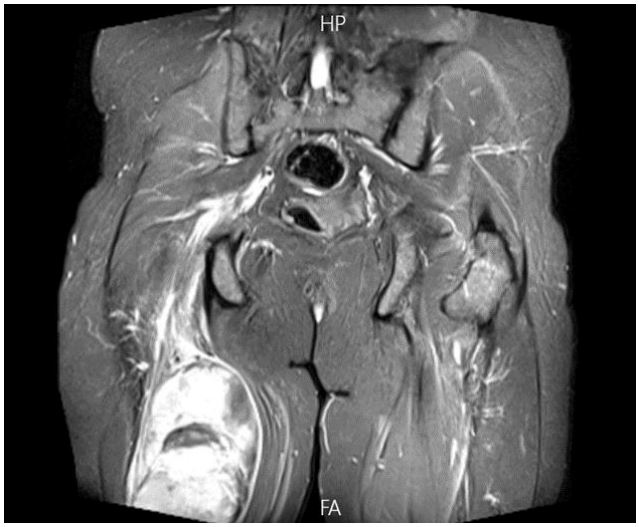

Figure 3. Pelvic MRI, T1, Coronal, Thigh mass

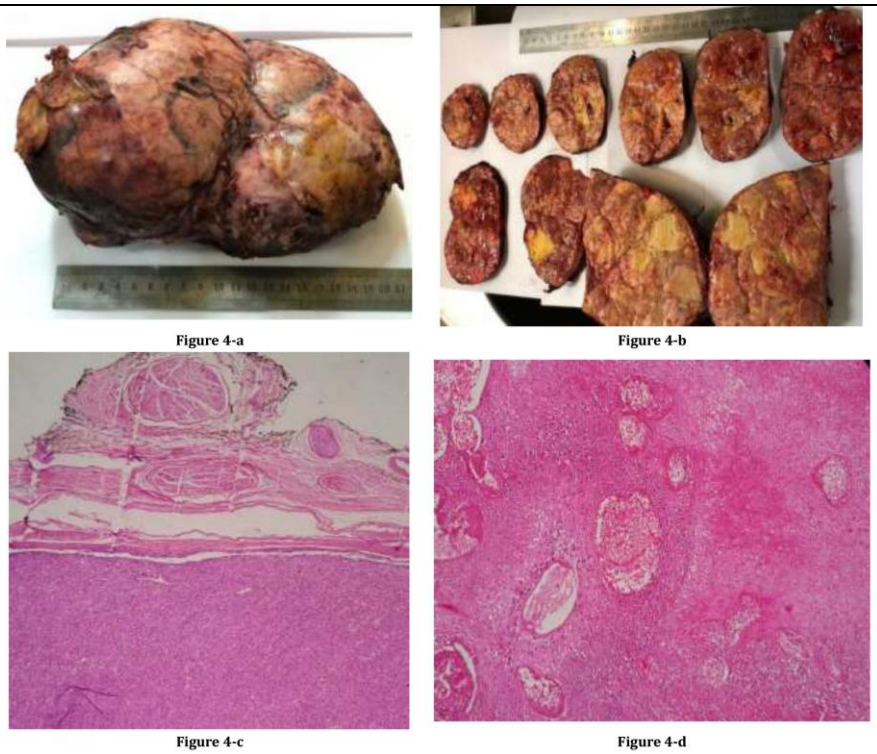

Figure 4-a and 4-b. Thigh tumoral mass - Macroscopic view: Huge pseudo-encapsulated ovoid tumoral mass, gray/tan in color and fleshy consistency with large foci of necrosis
Figure 4-c. Pseudo-encapsulated spindle cell sarcoma with adjacent hypertrophic nerve trunks (low power field)
Figure 4-d. Pleomorphic spindle cell sarcoma, ill-defined cytoplasmic borders, coarse nuclear hyperchromasia (medium power field)

After complete surgical removal, the patient was planned to undergo combination chemotherapy with Gemcitabine plus Paclitaxel. On the follow-up visit after two months, the patient had a good general condition without further complications. Her ESR was decreased to 42 mm/h, and her CRP was normal. Since she did not have dysmenorrhea and abnormal uterine bleeding, her uterine myomas were followed by Sonography without specific medical or surgical intervention. On the follow-up Sonography, multiple myomas were detected without growing in size. The patient will continue the chemotherapy until the end of the treatment course.

3. Discussion

NF-1 is a neurocutaneous disease with a special predisposition to tumorigenesis due to genetic mutations, affecting the tumor regulator systems. The disease is inherited in an autosomal dominant fashion in about 50% of cases, and half of cases carry de-novo mutations (1-4). The birth incidence rate of NF-1 is approximately 1:2600 to 3000, and its prevalence is about 1:5000 (3, 9-11). Initiative clinical sign usually is café-au-lait macules, after that, patients present with axillary and/or inguinal freckling, Lisch nodules, and neurofibromas, in descending order (9). The mentioned case was diagnosed as NF-1 since childhood based on the cutaneous manifestations, and now the patient fulfills four components of the criteria, including more than six café-au-lait macules, several neurofibromas, axillary and inguinal freckling, and more than two Lisch nodules in both eyes. There was no known case of NF-1 among family members, and first-degree relatives did not have any suspicious manifestations; therefore, the patient seems to carry a de-novo NF-1 gene mutation.

Although cutaneous manifestations are usually the initiative signs, several patients do not notice cutaneous lesions and take them seriously until the presence of complications of the disease. Xie et al. reported a case of a 39-year-old woman with NF-1-associated multiple rectal neuroendocrine tumors who was presented complaining of intermittent hematochezia (4). Similarly, Bayram et al. reported a 17-year-old man admitted due to sub-acute progressive left limb paresthesia, and the patient was finally diagnosed as NF-1 with multiple plexiform neurofibromas (2). Along with cutaneous manifestations, NF-1 presents with a wide spectrum of signs and symptoms involving the eyes, central and peripheral nervous system (CNS and PNS), cardiovascular system, and skeletal system. Ocular manifestations include Lisch nodules and Optic Pathway Gliomas (10). An ophthalmologic examination of our patient showed Lisch nodules in both her eyes; however, she did not have any signs and brain MRI findings in favor of OPG.

Neurologic abnormalities include CNS- and PNS-related tumors and their associated symptoms, headache, cognitive deficits, learning disabilities, seizures, macrocephaly, and peripheral neuropathy (12, 13). Our case was presented with headache, peripheral neuropathy, and progressive muscle weakness, especially in the pelvic girdle, but she never had seizures. Moreover, the patient had a few bright spots on the brain MRI which are common in children with NF-1, and they may disappear through time but in our patient, they are still present in adulthood. Bright spots are not malignant or pre-malignant lesions (9). Cardiovascular abnormalities of NF-1 patients include a variety of congenital heart diseases, including pulmonary and mitral valve anomalies, septal defects, and tetralogy of Fallot (14). Essential hypertension is prevalent among NF-1 patients.

Furthermore, hypertension might be secondary to renovascular lesions and even patients who are still normotensive might have an underlying lesion (9, 15). Our patient did not have any cardiac abnormality on the echocardiographic evaluation, and her systolic blood pressure never raised over 110 mmHg. The patient's blood pressure should be monitored on future follow-up visits for the possible development of hypertension. NF-1-associated bone abnormalities include bone dysplasia (initially manifest as anterolateral bowing of the tibia), pseudoarthrosis, decreased height growth during puberty, osteoporosis, scoliosis, and other vertebral defects (16). Our patient had severe scoliosis and kyphosis. Cervical and thoracic spine MRIs detected multi-level disc dehydration, degeneration, and disc osteophyte complexes. She had also leg bowing; however, she did not have any specific signs of pseudoarthrosis, osteoporosis, and osteopenia.

The special point about the reported case is the simultaneous presence of multiple tumoral lesions, including retroperitoneal mass, multiple uterus myomas, and the mass lesion in the posterior aspect of the right thigh. The histopathological evaluation of the biopsy from the thigh mass was suggestive of MPNST. The retroperitoneal and the thigh masses were excised by surgery and histopathological evaluation of both masses confirming the diagnosis of MPNST.

Regarding the predisposition of NF-1 patients to tumorigenesis and the high prevalence of peripheral nerve tumors among these patients, any masses changing their character like rapidly enlarging masses and changes in the severity of the pain or associated neurologic deficits should raise suspicion for malignancy. One of the serious malignant lesions is MPNST. MPNSTs are also associated with radiation. Radiation-related and sporadic MPNSTs are usually detected among the elderly, while NF-1-associated MPNSTs usually present in the third to fourth decades of life same as the reported case (17). According to the

study by Stucky et al., the most common site for MPNSTs is the extremities, and after that, the trunk is another common site (18). Head/neck is a less common location, and there are a few reports of MPNST of the oral cavity as rare clinical cases (7). Our case had two confirmed MPNSTs on both common sites (trunk and extremity).

The most beneficial method for the detection and localization of all NF-1-associated tumors, especially MPNSTs, is MRI which shows the local extensions and the position of mass in relation to adjacent nerves. MRI cannot be helpful in determining whether a lesion is benign or malignant. A biopsy along with histopathological evaluation can confirm the exact type of tumor. Accordingly, the patient underwent brain, cervical, thoracic spine, abdominal, and pelvic MRI for the detection of possible tumors with their accurate location and extension. Two suspicious masses were detected in imaging studies. Regarding its location, a core needle biopsy was performed from the thigh mass since it was possible to do a biopsy before surgical intervention and its pathological examination was suggestive of MPNST. Finally, both masses were excised and sent for histopathological evaluation, which confirmed the diagnosis of MPNST. MPNSTs are usually large and firm masses containing areas of necrosis and hemorrhage on macroscopic pathologic examination and highly cellular spindle cells on microscopic examination (19). Both excised masses had the typical macroscopic and microscopic appearance for MPNSTs.

Surgery is the treatment of choice for most NF-1-associated tumors, including MPNSTs; however, sometimes, surgical resection is not possible due to the tumor location, adjacent structures, and its extensions (3, 20). Regarding multiple masses and two MPNSTs, our patient was planned to undergo combination chemotherapy with Gemcitabine plus Paclitaxel.

4. Conclusion

NF-1 patients are at a higher risk for developing benign or malignant lesions than the general population; as a result, any suspicious symptoms, including significant fatigue and weight loss, mass sensation, neurological deficits, and any masses changing their character, should prompt evaluation for possible malignancy. Timely diagnosis and treatment by surgical excision with subsequent chemotherapy or radiotherapy is the mainstay of patient management.

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Footnotes

Conflicts of Interest: Authors declare that there are no conflicts of interest regarding the publication of this article.
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