CASE REPORT

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A Rare Tumor in a Patient with Neurofibromatosis Type 1: Humerus Osteosarcoma

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ABSTRACT Neurofibromatosis type 1 (NF1), also known as Von Recklinghausen disease, is an autosomal dominant inherited genetic syndrome with a predisposition for a wide range of benign and malignant tumor development. Although many kinds of tumors develop in NF1 patients, osteosarcoma is seen very rarely. We report an unusual case of a 19-year-old NF1 male suffering from osteosarcoma in his humerus. The patient developed a huge mass and pathologic fracture in his left upper arm. Besides, multiple bilateral mainly ossified millimetric pulmonary metastatic lesions were detected on his chest computed tomography. In the current manuscript, we present this patient with NF1 associated osteosarcoma and review the literature.

Keywords: Neurofibromatosis type I; osteosarcoma; calcified pulmonary nodules

Neurofibromatosis type 1 (NF1), also known as Von Recklinghausen disease, is an autosomal dominant inherited genetic syndrome with a predisposition for wide range of benign and malignant tumor development. It is caused by mutation in the neurofibromin 1 gene located on chromosome 17q11.2.[1] NF1 is one of the most common dominantly inherited genetic disorders, occurring with an incidence at birth of approximately one in 3,000 individuals.[2] The patients with NF1 are presented with multiple café au lait spots, axillary and inguinal freckling, multiple discrete dermal neurofibromas and iris hamartomas known as Lisch nodules. An important consequence of the syndrome is the predisposition to a wide variety of tumors due to the inactivation of the NF1 tumor suppressor gene.[3] To the best of our knowledge, osteosarcoma has been reported very rarely, although various tumors develop in NF1 patients.

The aim of this case report is to present a patient with humerus osteosarcoma associated with NF1.

CASE REPORT

A 19-year-old male patient was presented to our hospital with complaints of generalized pain and extensive swelling in the left upper arm. The patient was diagnosed with NF1 according to the diagnostic criteria for NF1 and genetic tests during infancy. There was a consanguineous marriage between his parents and his father also had cafe-au-lait spots.

The physical examination revealed multiple characteristic cafe-au-lait spots and cutaneous neurofibromas on his whole body. The patient was referred to a radiologic evaluation. Radiography of the left humerus showed a displaced midshaft fracture and increased radiodensity around the fracture (Figure 1A). Coronal computed tomography (CT) image demonstrated a giant, lobulated, calcified mass lesion in the left upper arm (Figure 1B).

On magnetic resonance imaging (MRI), the lesion extending from the neck of the humerus to the distal diaphysis, measuring 212x100x85 mm caused

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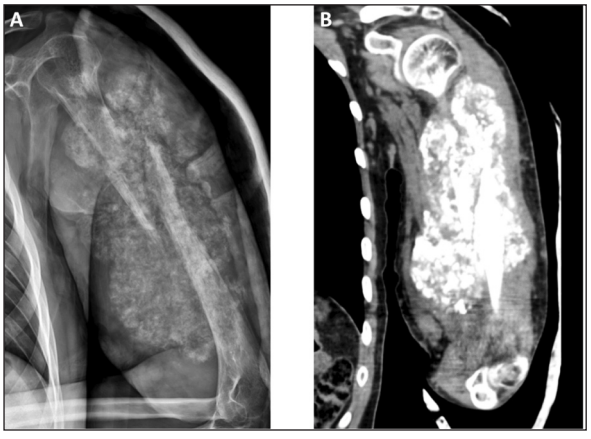

FIGURE 1: A) Radiograph of left humerus showing a displaced midshaft fracture, surrounded by a high density lesion. **B)** Coronal computed tomography image demonstrating a giant, lobulated, calcified mass lesion around the fracture in the upper arm.

displacement and angular, pathological fracture in the humerus diaphysis. Adjacent triceps and biceps muscles were infiltrated by this huge lesion (Figure 2A, Figure 2B). Contrast-enhanced MRI of the left upper arm revealed a marked heterogeneously contrast-enhanced mass with a cystic necrotic appearance in the central part (Figure 2C).

In addition, on his non-contrast chest CT, we detected multiple bilateral mainly ossified millimetric pulmonary lesions consistent with pulmonary metastasis of osteosarcoma (Figure 3). A percutaneous core biopsy of the mass demonstrated a high grade osteoblastic osteosarcoma (Figure 4). The patient refused all types of treatment and surgery.

Consent for publication: Written informed consent for publication of medical photographs was obtained from the patient's family.

DISCUSSION

A previous study has been indicated that the risk of developing malignant tumors in patients with NF1 is fourfold more than the normal population (confidence interval: 2.0-7.1).[4] Malignant connective tissue tumors such as malignant peripheral nerve sheath tumors, neurofibrosarcoma, malignant neurilemmoma, spindle cell sarcomas; brain tumors (gliomas, astrocytomas) such as optic nerve glioma, juvenile pilocytic astrocytoma, diffuse brainstem glioma; pheochromocytoma and paragangliomas are the relatively common malignancies developing in patients with NF1.[1,5,6] However, there are no convincing data in the literature, except for a limited number of case reports about the association between NF1 and bone tumor development. Moreover, the genetic relationship has not been identified between osteosarcoma and NF1 yet.

Chowdhry et al. reported four patients of 2,900 with osteosarcoma who had coexisting NF1. In this study, osteosarcomas were detected in typical locations such as distal femur, proximal humerus and

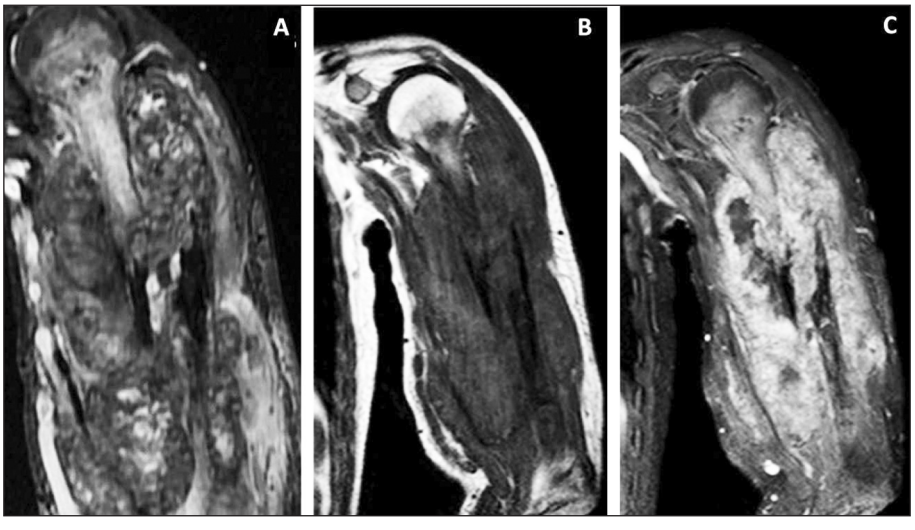

FIGURE 2: Coronal T1 weighted **(B)**, fat saturated **(A)**, and postcontrast **(C)** images demonstrates a marked heterogeneously contrast-enhanced mass with cystic necrotic appearance in the central part which infiltrated the adjacent triceps and biceps muscles.

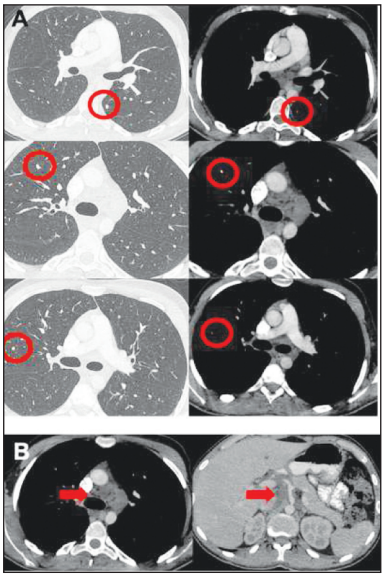

FIGURE 3: A) Axial computed tomography scans obtained with lung and mediastinum window settings show multiple metastatic nodules some of which contain calcifications in both lungs. **B)** Multiple neurofibromas, components of neurofibromatosis type 1, are observed in the mediastinum and upper abdomen (mediastinal window setting).

proximal tibia in patients with NF1. Two of the four osteosarcoma patients developed lung metastases.[7] In an article about malignancies in Chinese patients with NF1, there was detected just one osteosarcoma around twenty patients who developed malignancies between 123 NF1 patients. It was telangiectatic osteosarcoma located in the distal femur, a typical location.[1]

Hatori et al. described a case of osteosarcoma in the proximal femur arising at the previously excised malignant peripheral nerve sheath tumor.[8] Another reported case was a patient with NF1 with parathyroid adenoma and mandible osteosarcoma accompanying hyperparathyroidism. Since parathyroid hormone is a modulator of osteoblastic activity, it has been claimed that hyperparathyroidism can lead to induction and growth of osteogenic sarcomas.[9] To our knowledge, this was the only atypical location of osteosarcoma in a patient with NF1.

Although our patient was diagnosed with NF1, the lesion is thought to be a bone tumor rather than a soft tissue tumor, as there were many accompanying calcified pulmonary metastatic nodules. According to the age of the patient, mainly the malignant bone tumors as Ewing sarcoma and osteosarcoma were considered. Eventually, we evaluated this mass as osteosarcoma according to its radiological features.

In conclusion, despite its rare occurrence, osteosarcoma should be taken into account in patients with NF1, particularly those with pathologic fractures and concomitant findings.

Learning points: Although a variety of malignancies may accompany to neurofibromatosis, osteosarcoma is a very rarely seen tumor of them, so clinicians and radiologists must be aware. This case also had an uncommon location. Osteosarcomas

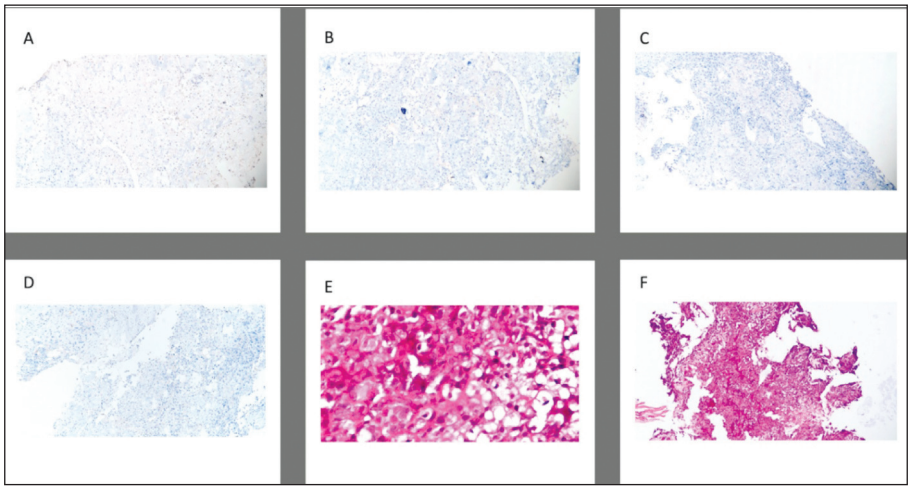

FIGURE 4: A) Actin, original magnification x10. **B)** Desmin, original magnification x10. **C)** S-100, original magnification x10. **D)** pan-CK, x10. **E)** H&E stain, original magnification x40. **F)** H&E stain, original magnification x10.

favor proximal humerus and on the contrary, our case was placed after the proximal 1/3 of the bone.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Melis Koşar Tunç, Hülya Kurtul Yıldız;* ***Design:*** *Damla Karabıyık, Melis Koşar Tunç;* ***Control/Supervision: Data Collection and/or Processing:*** *Deniz Özel, Melis Koşar Tunç;* ***Analysis and/or Interpretation:*** *Okan İnce;* ***Literature Review:*** *Melis Koşar Tunç;* ***Writing the Article:*** *Melis Koşar Tunç, Deniz Özel;* ***Critical Review:*** *Okan İnce;* ***References and Fundings:*** *Melis Koşar Tunç;* ***Materials:****Melis Koşar Tunç.*

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