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Case Report

High grade osteosarcoma on a background of trichorhinophalangeal syndrome: A family perspective



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ABSTRACT

Trichorhinophalangeal syndrome (TRPS) is a rare genetic disorder with typical craniofacial and skeletal abnormalities. Three main subtypes have been described. All variations of the condition affect the hair (tricho), nose (rhino) and fingers (phalangeal). The diagnosis is usually made through clinical examination augmented by hand radiographs that reveal characteristic cone-shaped epiphyses

Sporadic case reports detailing TRPS have been described in the literature. We describe the first report of high-grade osteosarcoma presenting in two members of the same family with trichorhinophalangeal syndrome (TRPS).

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1. Case

A 21-year-old man presented with a three month history of pain and a lump on his left distal femur. As a child, pediatricians reviewed him because of his short stature. It was noted that he exhibited the classical phenotypic characteristic of TRPS; short stature, very sparse hair with reduced hair growth, and cone shaped epiphyses on imaging. Furthermore, both his sister and mother also had the same distinctive appearances. The pediatricians therefore diagnosed our patient, along with his sister and mother, with an autosomal dominant inherited form of TRPS. He had no other significant medical history.

On presentation to our unit, plain radiographical images of his left femur revealed a central, rapidly expanding lesion within the distal femur remote from any pre-existing exostoses. Magnetic resonance imaging (MRI) of the left femur showed an 8 centimeter tumor arising in the distal femoral meta-diaphysis with a small soft tissue component.

Needle biopsy showed an infiltrative high-grade, spindle-cell sarcoma. Although there was no convincing osteoid the features were suggestive of osteosarcoma. Staging showed no evidence of metastasis and bone scan confirmed the lesion was solitary.

Two months after referral, our patient was undergoing chemotherapy consisting of cisplatin, doxorubicin and methotrexate, when his mother complained of an ache to her right distal femur. Plain radiographs and MRI revealed a rapidly expanding lesion within the right distal femur. A needle biopsy confirmed the diagnosis of a high-grade, osteosarcoma identical to the features seen in the distal femoral tumor of her son.

Cytogenetic analysis of both our index case and his mother's femoral biopsies by array comparative genomic hybridization using BlueGnome 0.5 M Cytochip v3.0 BAC array showed whole chromosome gain of 3, 9 (possibly 2 copies), 11, 14, 15 and 22. Segmental or interstitial gains included 3p21 (possibly amplified or higher level gain), 4p, 5p, 12p, 16p13.2-q13.12, 16q12.1-q13, 17p11.2, 17q21.33-q25, 18pter-p11.21 and 21q11.2-q21.1. Whole chromosome losses included chromosomes 1, 2, 6, 8, 10 and 13. Segmental losses included 16q13-q22.1, 17pter-p12 and 18q.

Staging CT of the patient's mother did not show any soft tissue metastasis but, unfortunately, a bone scan revealed a further, asymptomatic bony lesion within the left distal femur. This was confirmed as another high-grade osteosarcoma on needle biopsy. Chemotherapy was therefore initiated in the form of cisplatin, doxorubicin and methotrexate.

They both underwent three cycles of chemotherapy prior to surgical resection of the tumor and distal femoral replacement. The mother elected to have the symptomatic right distal femur operated on first and, at a later date, and after suitable recovery, the left.

Histological review of both our index case and his mother's resection specimens revealed 99% post chemotherapy tumor necrosis.

Postoperative chemotherapy was initiated in both patients. Sadly, prior to undergoing resection of the asymptomatic left femur, the index case's mother died as a result of chemotherapy complications.

Because of the strong link between TRPS in our family cohort and osteosarcoma the index case's sister was screened using a bone scan. This did not reveal any abnormality but regular follow-up is planned.

2. Discussion

Trichorhinophalangeal syndrome (TRPS) was first described in 1966 by Giedon who delineated a syndrome characterized by

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sparse and slowly growing hair, a long pair shaped nose with a bulbous tip, and finger deformities [1]. Since Geidon's first descriptions of TRPS, only subsequent small cases series have been published detailing further phenotypical characteristics along with attempts to specify the genetic abnormalities.

TRPS can be subdivided into three sub-types with the above key features expressed in all three [2,3]. The syndrome can have multi-system involvement with associated endocrine disorders, renal alterations, heart anomalies and bone dysplasia [1–4].

TRPS I and III are inherited in an autosomal dominant fashion, while TRPS II are often sporadic cases [4]. Deletions, insertions and translocations of chromosome 8, specifically from 8q24.11 to 8q24.13 resulting in haploinsufficiency of a specific zinc finger protein that is a putative transcription factor have been indicated as the causative genetic abnormality [5–7]. In addition to the genetic anomalies for TRPS I, TRPS II is caused by a further mutation in the EXT1 gene that spans the TRPS I locus resulting in multiple cartilaginous exostoses [8–10]. No further cytogenetic abnormalities have been described in TRPS III; supporting the theory that TRPS III is on the severe end of the same spectrum as TRPS I [2].

The diagnosis and sub classification of TRPS is, however, based on clinical and radiological findings, supported by genetic analysis in equivocal cases [4].

Orthopedic surgeons are likely to come into contact with these patients due to their bony deformities of the hands, femoral head and presence of multiple exostoses that may cause nerve impingement, joint mobility problems or extreme discomfort [11–13].

The benign exostoses in TRPS have a recognized malignant potential which have been shown to develop into chondrosarcomas [4,13]. Both our index case and his mother demonstrated *de novo* high grade osteosarcoma. To our knowledge, this occurrence has not been described anywhere within the literature.

Our cases highlight that TRPS in general also has the potential for *de novo* osteosarcoma. We would suggest plain radiographs and magnetic resonance imaging of the affected limb, along with staging bone scintigraphy and computer topography of the chest, abdomen and pelvis as the first radiological investigations of choice at any center managing a patient with a suspected sinister exostosis or bone pain in TRPS. Bone biopsy is the gold standard method of determining the exact nature of any bony lesion as it provides a tissue diagnosis. Biopsy should be performed at a reference bone tumor unit that is familiar with the care of musculoskeletal malignancies and where specialist orthopedic, radiology, oncology and histopathology expertise can be rapidly accessed under the auspices of a fully accredited bone sarcoma multi-disciplinary team.

We would advocate that any unit treating a patient with TRPS who has a suspect bone malignancy follow published guidelines for the management of bone sarcoma [14].

No recommendations have been published regarding the long term surveillance of patients with TRPS. Follow-up should take into account the multi-systemic involvement of the syndrome and any potential malignant transformation within a pre-existing exostosis or, as in our cases, *de novo* malignancy, should be recognized early thereby promoting the possibility of limb salvage surgery as a viable, curative option.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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