

11368 - Genetics in orthopaedic Oncology - Sarcoma with Challenging Pedigree of Li Fraumeni Syndrome: First Case Study from India.

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Background/Objective: Sarcomas, a rare cancer of mesenchymal tissues, affecting a small portion of the general population remain a challenging disease to treat. The incidence of bone and soft-tissue sarcomas represents 11% of all cancers among adolescents and young adults. In general as a clinician there are standard set of sarcoma prognostic counselling. Its unusual to get a pedigree of different cancer patients. While most sarcoma patients do not have a striking family history of cancer, sarcomas are common manifestation of cancer predisposition syndromes such as Li Fraumeni which could be heritable or a germline genetic abnormality. Here we report a case of a 43 years old male who presented with right gluteal pain and a significant weight loss. PET CT evaluation revealed progression of large soft tissue mass in the osteolytic lesion of right anterior iliac bone and a metabolically active osteolytic lesion in the right proximal sacrum, left scapula and right 5th and 7th ribs. A CT guided core biopsy showed a tumor composed of groups of large cells, which were positive for Vimentin (diffuse), and patchily for Bcl2, CD34, and EMA and negative for p53, ALK-1 and Myf4 confirming pleomorphic undifferentiated sarcoma (high grade). Patient received appropriate chemo regimens but as the disease was progressive and the proband had a strong family history of malignancies, a hereditary cancer predisposition test using Next Generation Sequencing was also performed. No case of LiFraumani was reported from India when searched in pubmed.

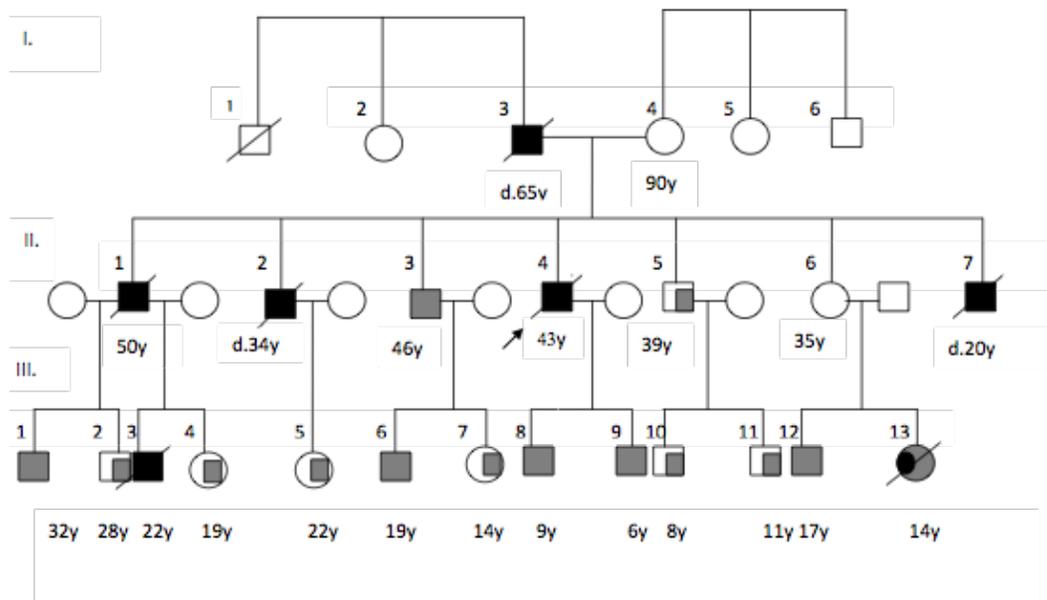
Methods: On patient's consent, genomic DNA isolated from saliva of the proband was used for preparation of the 'DNA sequencing-ready' library, which involves target sequence enrichment for 86 unique genes associated with hereditary cancers, which include genes recommended by ACMG (American College of Medical Genetics and Genomics) in an IRB-approved protocol. The generated library was subjected to NGS on the MiSeq platform. Genetic variations were identified by using the STRAND[®] NGS software and interpreted using StrandOmics[™] platform.

Results: NGS analysis of the patient revealed a likely pathogenic, heterozygous germline mutation (c.323delG; p.Gly108ValfsTer15) in exon 4 at codon 108 of the TP53 gene (RefSeq id: NM_000546). This specific mutation with the presence of strong familial history of hereditary cancer met the clinical criteria of classic Li Fraumeni

syndrome (LFS) that prompted genetic testing of this mutation in proband's other family members (n=15). The family study protocol included compilation of a detailed family history of malignant disease of all anatomic sites. In segregation analysis of the kindred, the same mutation was detected in eight of family members among which one who was affected with brain tumor and the other with osteosarcoma have succumbed to the disease very recently. Other family members, being positive and likely pathogenic for the germline p53 mutation have not been identified with any expressed phenotype (Pedigree chart is shown below). Genetic counseling was provided before sample collection and at disclosure of results.

Conclusions: This is the first known case report from India highlighting undifferentiated sarcoma with a phenotype of the LFS. LFS is a relatively rare disease entity and patients with LFS are at a high risk to develop early-onset breast cancer and multiple malignancies, among which sarcomas are the most common. We are carefully selecting sarcoma prone families based on their challenging pedigree to illustrate etiologic part of hereditary variables alongside phenotypic and genotypic heterogeneity encountered in such families to help early diagnosis, surveillance, and proper management.

Pedigree chart



-  = p53 mutated, phenotypically unaffected
-  = p53 wild type
-  = affected male individuals, with sarcoma
-  = affected male individual, with undifferentiated sarcoma
-  = affected female individual with brain tumor
-  = proband
-  = death