Tumor Syndromes Predisposing to Osteosarcoma

Osteosarcoma (OS) is the most common primary bone tumor with bi-modal age distribution predominantly occurring in adolescents and a small second peak in the elderly (1). While the vast majority of osteosarcomas are sporadic, a small percentage occurs as component of hereditary syndromes. The known Osteosarcoma predisposition syndromes are as follows: Li-Fraumeni syndrome (LFS), Retinoblastoma (RB), Rothmund-Thompson syndrome (RTS Type 2), Werner Syndrome (WS), Bloom syndrome (BLM), RAPADILNO syndrome and Diamond Blackfan Anemia (DBA).

Li-Fraumeni Syndrome (LFS)

Described in 1969 by Drs. Frederick Li and Joseph F. Fraumeni Jr, this hereditary cancer predisposition syndrome is associated with sarcomas, breast carcinoma, brain tumors, leukemias and adrenocortical carcinomas (2). LFS is an autosomal dominant disorder and is characterized by germline mutations in TP53 gene (3, 4). Classic Li-Fraumeni criteria include proband diagnosed with sarcoma before age 45, has first –degree relative with any cancer before age 45 and another first or second degree relative with any cancer before age 45 or sarcoma at any age (2). About 250 mutations throughout the gene have been detected, majority occurring within the DNA binding domain (DBD) (5, 6).

The most common sarcoma in LFS is osteosarcoma accounting for about 12.6% of the cases (7). While the presentation is similar to sporadic osteosarcoma with metaphysis of long bones as the most commonly affected site, age at presentation can be younger than in general population(8). Histological features are similar to conventional osteosarcomas and the tumor is composed of pleomorphic tumor cells containing variable amounts of osteoid matrix and can be sub typed as osteoblastic, chondroblastic and fibroblastic types depending on the predominant matrix produced by the tumor (2). The earlier age of onset at successive generations (genetic anticipation) is attributed to telomere attrition and a role for higher mutator phenotype in successive generations(9). The most common TP53 mutations in sarcoma patients of LFS are missense mutations (72.8%) and involve codons 273,248,282,175 and 220 in the DNA binding domain (DBD)(8). High prevalence of codon 245 and 282 were seen in osteosarcoma whereas more than 20% of all mutations are seen at codon 273 in patients with rhabdomyosarcoma(8). Mutations outside the DBD (codons 337 or 344) are associated with leiomyosarcoma and unlike osteosarcoma and rhabdomyosarcoma, frameshift, splice –site and nonsense mutation are more frequent. It is postulated that mutations predicting absence of wild type protein lead to late-onset type sarcoma and missense DBD mutations accumulating mutant proteins give rise to early onset types of sarcoma such as osteosarcoma and rhabdomyosarcoma(8).

Hereditary Retinoblastoma:

Hereditary retinoblastoma is a rare autosomal dominant disorder of infancy caused by biallelic mutation of the RB1 gene in a developing retinal tissue. Inherited mutation of RB1 in one allele is a predisposing factor for the development of retinoblastoma following the mutation of the second allele (10, 11). This hypothesis termed as “the two-hit hypothesis” put forth by Alfred Knudson in 1971 was based upon statistical analysis of hereditary and spontaneous retinoblastoma cases (12). RB1 gene is a cell cycle

regulatory gene and homozygous RB1 mutations are embryologically lethal(13). In recent years the cure rates of >90% has been achieved for patients with retinoblastomas (14). However, children with retinoblastoma are at increased risk of developing subsequent malignancies, especially osteosarcoma at a later time and also more susceptible to develop these tumors following radiation (15). RB1 is located at ch13q14.1 and consists of 27 exons encoding a 105 KD RB1 protein (16). The spectrum of RB1 mutations are distributed throughout the gene and include missense mutations, indels, promoter and splicing mutations and also epigenetic changes such as promoter methylation(17). The incidence of somatic RB1 mutation in osteosarcoma ranges between 30-75% (18). In hereditary retinoblastoma patients there is a 400-fold increase for developing osteosarcoma related to both genetic susceptibility and radiation therapy(15). The age incidence is similar to sporadic osteosarcoma affecting adolescents and young adults. Unlike LFS there are no established guidelines for surveillance for secondary malignancies in retinoblastoma survivors. In one study (19) favorable outcome has been reported in second primary osteosarcomas of extremity in retinoblastoma survivors.

Osteosarcoma Predisposition and RecQ DNA Helicases:

RecQ helicases are proteins that are necessary for unwinding of double stranded DNA during replication and repair and thus are important for maintaining genomic integrity (20). There are 5 RecQ helicases and mutations in three of them (RecQL4, BLM, WRN) are associated with Rothmund-Thompson, Bloom and Werner syndromes respectively. All 3 are cancer predisposition syndromes. RecQL4 is also mutated in RAPADILINO syndrome.

Rothmund –Thompson Syndrome (RTS)

Rothmund-Thompson syndrome belongs to RecQ helicase associated autosomal recessive disorders strongly associated with osteosarcoma predisposition(21). Two types of RTS have been described (RTS Type 1 and RTS Type 2). Type 2 RTS is caused by mutations of RecQL4 helicase (ch 8q24) and predisposes to osteosarcoma and skin cancer development (22). The syndrome is characterized by poikiloderma, sparse hair, frontal bossing, saddle nose, short stature, radial defects, hypoplastic patellae, esophageal or pyloric atresia, annular pancreas, myelodysplasia and cataracts(21). Types of mutations in RecQL4 include nonsense, frameshift, splice site and intronic deletions (23). Unlike other TP53 and RB mutated syndromes, RecQL4 mutations are not seen in sporadic OS (23). In a review of 61 patients with RTS by Stinco et al(24), OS accounted for 62% of cancers, of which 3 were multicentric (metachronous) and 12 developed before the age of ten. An association of gene truncation mutations with development of OS has been proposed by some authors (25). Histological subtypes described are similar to conventional OS and multimodality chemotherapy has been recommended as treatment of choice (26) based on outcome on a series of 7 patients. A second syndrome caused by RecQ4 mutations and predisposition to OS is RAPADILINO syndrome(21). The name is the acronym for: RA: Radial dysplasia; PA: Patella aplasia or hypoplasia and left high arched palate; DI: Diarrhea and Dislocated joints; LI: Little size and Limb malformations; NO: long, slender Nose and NOrmal Intelligence)(21).

Werner Syndrome (WS)

Werner syndrome is an autosomal recessive disorder; also known as adult progeria

characterized by premature aging, short stature, bilateral cataracts and scleroderma-like skin changes(27). These patients are predisposed to many types of neoplasia including osteosarcoma, soft tissue sarcoma, meningioma, myeloid disorders, melanomas, thyroid carcinomas among others (27). High prevalence is noted in the Japanese, presumably related to founder effect (27). OS occurs at a later age, usually in the fourth decade(21). WS is caused by mutations occurring at WRN gene, belonging to the RecQ family(21). OS in WS cases have atypical distribution affecting predominantly foot, ankle and patella (28). They are treated similar to conventional osteosarcoma(21).

Bloom Syndrome (BLM):

Bloom syndrome is an autosomal recessive disorder characterized by short stature, sun-sensitive rash and sparseness of subcutaneous fat in infancy and childhood(21). Mutations in BLM gene which is a RecQ helicase was discovered in 1995 (29). While majority of the cancers in BLM are carcinomas, leukemias and lymphomas, the osteosarcoma rate is higher than general population(30). The prevalence rate in Ashkenazi Jews is 1% and osteosarcomas are treated by standard regimens(31).

Diamond Blackfan Anemia (DBA)

Diamond Blackfan Anemia is a clinically and genetically heterogeneous disease characterized by pure red cell aplasia manifested at early infancy, congenital abnormalities (craniofacial, thumb, heart, renal) and predisposition to cancer(21). Disease causing mutations are seen in Ribosomal S19 and other ribosomal proteins (32). Six cases of OS have been reported among 700 DBA patients(33) .

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