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A review on lipoma and its genetic interventions

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ABSTRACT

Lipomas are benign soft tissue fatty tumours that most commonly appear in the third decade of life when fatty tissue accumulates. Histologically, lipoma is composed of mature fat cells with a thin fibrous capsule. Simple lipomas account for 80% of adipose tissue tumours. The aetiology may be genetic like Familial Multiple Lipomatosis. Some tumours, like the well differentiated Liposarcomas never metastasize unless they undergo de-differentiation. They can be introduced as Atypical Lipomatous Tissue, ALT. Southern blot analysis is performed by obtaining DNA from ALT, cases in which most of them are characterized by the presence of supernumerary ring and long marker chromosomes. The complex chromosome region contains genes MDM2, CDK4, HMGI- C, SAS, GLI, CHOP, OS4 and OSP. Most of ALTs, after analysis revealed amplification of CDK4 and MDM2 proto- oncogenes that play major role in permitting over ride of block operated on cell proliferation. Immuno-histochemical results have shown MDM2 over expression in about 50% of ALTs along with weak CDK4 immuno-positivity. Also the lipomas with Gene fusion transcripts have the expression of certain genes, HMGA2/LPP, HMGA2/RDCI and HMGA2/NFIB. Of these 98% of cases were analyzed for the possible expression of HMGA2/LPP and LPP- HMGA2 fusion genes using reverse transcription polymerase chain reaction. Over all these cases, shows non-enhanced adipocyte apoptosis and enhanced adipogenesis in lipoma tissue. Thus studies provide insights into molecular pathogenesis of lipomatous tumour and representation of distinctive subset of mesenchymal neoplasms with mature adipocyte differentiation.

Keywords: Lipoma; liposarcomas; lipomatosis; adipogenesis; mesenchymal neoplasms.

INTRODUCTION & BACKGROUND

Lipomas are benign neoplasm of mesenchymal origin which are composed of mature adipocytes and encapsulated by a thin layer of fibrous tissue. They are found subcutaneously and felt superficially where they occur predominantly on abdomen, shoulder and upper back. Some are found in depth as intramuscular lipoma and also deep seated lipomas [1]. Lipomas affects mainly males and people within the age group of 40 to 60 years. It doesn't pose any threat to the patient unless they encroach joints, nerves or if they are rapidly growing. Though rare, they are associated with disorders such as multiple hereditary lipomatosis [2]. Some malignant tumors like liposarcomas poses a greater risk to the patient and is of important concern to be distinguished from lipomas. Also, Atypical lipomatous tumors (ALTs), the well differentiated liposarcomas never metastasize unless they undergo dedifferentiation.They develop on the soft tissues of limbs and in retroperitoneum. Morphologically lipomatous tumors are of three forms based on cytogenetic analysis, they are ALTs, myxoid and pleomorphic [3]. About half of all lipomas have aberrations in the chromosome 12q13-15 segment according to cryogenic analysis. Fluorescence in *in-situ* hybridization shows the chromosomal region 12q 13-15 is the amplified component within the long marker chromosomes of ALTs [3].

Epidemiology & etiology

The epidemiological and demographic factors are not very well defined. Lipomas are present only in 1% of the population and it has low risk factors unless it is formed on any organ and cause pain. However cytogenetic analysis have improved better diagnosis of the disease [4]. Lipomas befall in all age group i.e., from childhood to old age. But, however it's estimated that it mainly occur in an age group of 40 and 70 years. Moreover, the average age for well circumscribed subtype was 47.25 years and 51.5 years for Infiltrative subtype [5]. Exact gender distribution is not

yet known. But, nevertheless in some studies it shows a predominance of female getting affected. But, in contrast in majority of estimations reported the predominance I'd found out in males [4].

The exact aetiology remains unknown while an association with gene rearrangement of chromosome 12 is found in solitary lipomas with abnormality in HMGA2/LPP fusion gene. But another thesis states that lipoma can be due to trauma in a particular area. In one case, researchers have linked up to a fact that adipose tumor growth as a post traumatic event following a direct impact on the soft tissue. Some connections which can be bring about is that it can lead to glucose intolerance, obesity, liver disease etc. [6].

Pathogenesis

Anatomically, it's enclosed in a thin, fibrous capsule. Generally, they lie subcutaneously but in some cases they can be found in internal organs like Stomach, Bowels etc. They are composed of slow growing mature adipose tissue, lobulated having a minimal connective tissue trauma. Clinically, they are just mobile mass of tissue which can be felt under the skin and they are painless. But, rarely can they occur in muscles or organs and many cause pain. They are mostly harmless, and if wanted surgically excised if pain is felt. However, some people remove this for cosmetic reasons [7].

Treatment and prognosis

Lipoma is adequately treated by marginal excision to remove the fibrous capsule, which is described as shelling out of tumors, with minimal risk to surrounding normal blood vessels, nerves, muscles or bone. Wide excision is done for deep-seated Lipomas like intramuscular lipoma [8]. After surgical excision there is no probable chances of recurrence of the tumor that gives good prognosis. ALTs represent mesenchymal neoplasms with mature adipocytic differentiation. They never metastasize unless they undergo dedifferentiation. ALTs are characterized cytogenetically by the presence of supernumerary ring and long marker chromosomes with the chromosomal region 12q 13-15 as the amplified component within the marker chromosomes. FISH analysis demonstrates rings are composed of DNA sequences derived from 12q 13- 15 region. MDM2, CDK4, HMGI-C genes are involved in human tumorogenesis that play role in molecular pathogenesis of ALTs [9].

Genetic intervention

In certain cases, there is difficulty in distinguishing deep-seated Lipomas from cancers and lower grade cancers. Miss diagnosis in treatment plan of shelling out of the tumor, can spread the tumor if it is malignant. Biopsy is desirable before committing larger surgical procedures. Similar clinicopathological features found in lipoma and ALTs in certain cases [10].

Analyses Inquired to get in-depth of genetic roles for comparison are Immuno-histochemical Analysis, Southern Blot Analysis and PCR.

Reported methodologies

Along with 12 ALTs, 18 ordinary lipomas were recuperated for diagnostic examination and cytogenetic analysis that include immunohistochemical analysis and southern blot analysis. These analyses were acquired from the report work published by the researchers [11].

Immunohisto-chemical analysis

Utilization of monoclonal and polyclonal antibodies - anti MDM2 antibody IF2, anti MDM2 antibody SMP14 and anti-cdk4, antiserum SC260 assisted to carry out the analysis [12]. Immunostaining of the tissue sections could be enabled by a sensitive peroxidase- streptavidin method on formalin fixed, paraffin embedded material. Further a heat induced epitope retrieval method comforted to preheat the sections. Analyzation of HMGI-C expression and performance of absorption test for polyclonal antiserum C260 were previously done and also negative controls obtained by incubating the slides [11].

Southern blot analysis

From the 12 ALT cases retrieved 5 cases were suitable for southern blot analysis and the DNA suitable for the analysis were recuperated from these 5 cases. The suitable tissues were digested with EcoR1 restriction enzyme, fractionated by electrophoresis on 0.8 % agarose gel. With capillary blotting it was transferred to nylon membrane [11]. The following probes were radiolabelled by random priming with P^{32} CTP : a 369 bp fragment from the human HMGI-C gene, a 2.7 kb fragment from human c-mos, a 157 no fragment obtained by PCR from the human MDM2 gene, a 197 no CDK4 probe obtained by PCR using the following primers: CDK4S : GCTGCAGGTCATACCATCCT and CDK4A : CTCTCACACTCTTGAGGGCC. To prevent the overloading of DNA fragments in each lane, the c-mos probe was used as an internal control. Further, the densitometry analysis of autoradiogram determined the degree of amplification of the MDM2, CDK4, and HMGI-C genes [11].

PCR

This analysis was performed in an anticancer research done by researchers in Japan. Lipomas on surgical excision were obtained from 102 patients. MRIs and CTs helped to access the non adipose tissue component and the existence of thick fibrous septa [13]. Gd-DTPA injection for signal enhancement resulted in enhanced images. All tumors were diagnosed as lipoma [14]. After surgical excision, specimen were frozen, processed and cryopreserved and stored at -70iC. Synthesis of cDNA was confirmed by beta actin primers. PCR was then performed using a gene amplification of PCR system. The reaction conditions followed the below processes. Reaction mixture was heated for 3 min at 94iC followed by 30 cycles of 30s denaturation at 94iC, 30s annealing at 55iC, 30s extension at 72iC followed by one cycle of 7 min extension at 72iC. PCR products were electrophoresed on 1.5 % of agarose gel and visualized by ethilidium bromide staining [13].

REPORTED RESULTS

Immunohistochemical Analysis

MDM2: 80% of ALTs with over expression of mdm2 protein: while all ordinary lipomas were mdm2 negative. Cdk4: 100 % of ALTs with over expression of cdk4 and weak cdk4 immunopositivity in 11% of lipomas. HMGI-C: 83% of ALTs had HMGI-C immunopositivity and 44% of lipomas with positive immunoreactivity [15].

Southern blot analysis

Out of 5, 3 ALTs had amplification of cdk4, mdm2 and HMGI-C. HMGI-C was deleted in one case. Case 1 had amplification of all genes. Case 2 had amplification of cdk4 and signal was slightly increased in mdm2. While in cases 3 and 5 HMGI-C copy number were augmented and Case 4 reported deletion of HMGI-C.

PCR

With the help of the anticancer research done via PCR 23 cases were detected with gene fusion transcript of HMGA2/LPP, 2 cases with HMGA2/RDC1 and no cases with HMGA2/NFIB. From 102 cases 77 cases were fusion gene negative. 1% cases of positive gene fusion were not different from the 6.5% cases of negative gene fusion with thick fibrous nodular septa. And there were no pathological difference in positive and negative cases. Finally, one in both cases had bone and cartilage compartments.

DISCUSSION

A unique subset of mesenchymal neoplasms that has been designed by atypical lipomatous tumours which has been sketched by mature adipocytic differentiation. The presence of ring and/ or long marker chromosomes is the cytogenetic hallmark of these abrasions; these rings are mostly composed of DNA sequences derived from the 12q13-15 region that has been demonstrated by FISH analysis, this region of chromosomes is very complex. This region contains the genes that has significant role in human tumourogenesis. They include MDM2 (murine double minute 2), an important negative regulator of p53 tumor suppressor [16], CDK4 (cyclin dependent kinase 4), an oncogenes for cell cycle G1/S phase progression [17], HMG-IC (high mobility glycoprotein), significant in regulation of cell proliferation [18], SAS (sarcoma amplified sequence), involves in growth related cellular processes [19], GLI that mediates hedgehog (Hh) signaling [20], CHOP (C/EBP homologous protein) has role in ER- stress induced apoptosis [21], OS4 and OS9 [22]. The molecular pathogenesis of ALTs shows frequent gene aberrations for CDK4, MDM2 and HMG-IC via preliminary analysis. Another similar analysis also upgrades the significance of HMGA2 (HMG-IC), which encodes a protein belonging to a high mobility family, members of which are important in terms of the regulation of chromatin structure and gene expression is the target gene for rearrangements involving 12q13-15 [13]. Common molecular alteration with a putative role in the development of benign mesenchymal tumors is represented by the creation of chimeric genes derived from the fusion of HMGA2 gene with multiple partners. Therefore, the expression of certain genes analyzed on the lipomas with the gene fusion transcripts include HMGA2/LPP, HMGA2/RDC1 and HMGA2/NFIB of which 98 % of cases analyzed for the possible expression of HMGA2/LPP and LPP-HMGA2 fusion genes using a reverse transcription polymerase chain reaction [23].

Genes such as MDM2, CDK4, and HMGI-C that are involved in Human Tumorigenesis are proposed to play a role in the molecular pathogenesis of ALT [24]. Over expression of MDM2 which is called as Mouse double minute 2 homolog also known as E3 ubiquitin-protein ligase Mdm2 is a protein that in humans is encoded by the MDM2 gene. Mdm2 is an important negative regulator of the p53 tumor suppressor, represents a nuclear phosphoprotein was observed in about 50% of ALTs. Furthermore, a nuclear signal was detected in cases where gene amplification occurred. p53 which is also known as Tumor Protein activates transcription of MDM2 that binds to and inhibits the p53 trans activating domain. Blocks are seen on the cell cycle operated by the p53 gene which is been released by this auto regulatory negative feed-back loop shown by the gene. Stimulation of the E2F family and inhibition of pRb is been done by MDM2. The two main inhibitory systems of cell proliferation may be interfered that acts at the G1-S checkpoint as a consequence of over expression of MDM2. In variety of sarcomas Over expression and/or amplification of MDM2 have dealt with heterogeneous groups of lesions. A certain degree of tumour specificity maybe manifested through molecular aberrations occurred at the G1-S checkpoint hhas been in shown in an analysis of distinct subsets of soft tissue sarcomas which was an analysis that was conducted recently. With all these observations we can come up with the fact that among sarcomas, adipocytic tumours are most frequently targeted by MDM2, which is also known as E3 ubiquitin-protein [25].

In the cases studied about half of them viewed that Over-expression of CDK4 gene which represents the rudimentary molecular mechanism on gene amplification appears to be a consistent ending among ALTs when in contrast with ordinary lipomas. 33 kD protein which is characterized by catalytic kinase function is been encoded by CDK4 gene which is the Cyclin-dependent kinase 4 also known as cell division protein kinase 4 is an enzyme that in humans is encoded by the CDK4 gene. CDK4 is a member of the cyclin-dependent kinase family. pRb represents the target of members of the cyclin D family with which CDK4 gene form molecular complexes. With consequent up regulation of cell proliferation, pRb undergoes phosphorylation that leads to the release of the E2F family of transcription factors. G1-S cell-cycle checkpoint operates disruption of control over cell proliferation of which this contribution occurred due to molecular aberration that was due to with or without gene amplification of over expression of CDK4

gene, similarly, as described in melanoma cells these effects can be achieved by mutations of the catalytic domain of CDK4. In recent data's it was shown that atypical lipomas exhibited concomitant aberrations of both MDM2 and CDK4 indicating the existence synergistic permissive action over cell proliferation. SSCP analysis failed to reveal CDK4 mutations in the series of ALT analysed. Thus, ALTs once they undergo dedifferentiation they show the malignant property and uncontrolled cell proliferation showing these tumors are malignant [26].

The HMG proteins which are referred to as architectural transcription factors can bind to DNA and are involved in the organization of chromatin during DNA transcription as well as binding to DNA. They come under the high mobility group (HMG) family of non-histone nuclear proteins that codes for HMGI-C gene. The gene is generally associated with the acquisition of malignant phenotypes by neoplastic cells and is not detectable in normal human adult tissues and is highly expressed in developing embryos, is not detectable in normal human adult tissues [27]. Positive HMGI – C immono-reactivity were recognised to be in association with 12q13±15 chromosomal alterations which was seen in ordinary lipomas but the high immunopositivity was highly recognised in neoplastic cells compared to ordinary lipomas.

Overexpression of mdm2, cdk4 and HMGI-C leads to gene amplification which is also related with the formation of ring and giant marker chromosome. These over expressed proteins, represents the product of gene mapping in the 12q 13-15 chromosome region. HMGI-C amplification in ordinary lipomas indicate that HMGI-C aberrations may not be sufficient for malignant transformation. Even HMGI-C aberration appear to be in ALTs but MDM2 and CDK4 are targeted independently as they belong to distinct amplicones [28]. So HMGI-C rearrangement plays key role in the development of lipomas while MDM2 and CDK4 is associated with the pathogenesis in ALT.

So we can say that ordinary lipoma and ALTs may be part of same molecular genetics. But Lipomas are characterized by 12q13-15 rearrangements and HMGI-C activation while ALTs are with ring and giant marker chromosomes with 12q13-15 amplifications of HMGI-C, CDK4 or MDM2 and aberrant CDK4, MDM2 and HMGI-C protein expression [29].

It was also seen that the ubiquity of gene fusions involving HMGA2 in lipomas has increased, but clinicopathological characteristics based on different gene aberration is not corroborated. From the analysis of 102 lipomas, no cases expressed the fusion gene transcripts of HMGA2/NFIB while 23 cases had HMGA2/LPP and 2 cases had that of HMGA2/RDC1. A relation between the advancement of lipoma and obesity was indicated in several papers but there is no definitive data to support the correlation [23]. From the study we can set forth that obesity is not an associated factor in lipoma as there was no difference in BMI. A typical quality which could permit a correct diagnosis was a mass of homogeneous adipose tissue revealed from computed tomography and MR images of lipomas. But it may contain non adipose tissue which produce in homogeneous features on MRI [30]. Few percent of lipomas exhibit marked non adipose areas; these features can confound the correct imaging diagnosis as they may imitate findings related to liposarcomas. Recently it's reported that lipoma expressing HMGA2/LPP fusion gene transcripts showed heterogeneous signal enhancement along the thickened fibrous septaon MR images. But its questioned whether formation of non-adipose tissues in lipomas, is the responsibility of fusion genes. The comparison of involving HMGA2 revealed no difference on MRI concerning the prevalence of a thick fibrous septa and signal enhancement. Suggestions came that the HMGA2/LPP fusion gene may promote chondrogenesis supporting cartilage specific collagen gene expression through N- terminal DNA binding domains of HMGA2 [31]. Definitive pathogenesis for the development of non-adipose tissue components in lipomas is known but it's probably due to genetic alteration in addition to secondary effects. Enhanced diagnostic accuracy and a deeper understanding of a subset of bone and soft tissue sarcomas led by the detection of fusion gene-transcripts [13].

The molecular testing contributes to the diagnosis of lipomatous tumors. However studies found to express only 24.4% of lipomas with fusion gene transcripts. Chromosomal analysis by CHAMP study group reported that 22% of cases had a normal karyotype and the remaining karyotypically heterogeneous [13].

Investigations is necessary to increase diagnostic accuracy and to improve our knowledge of the etiology of lipomatous tumors.

CONCLUSION

All those analyses explains the virtual absence of benign lipomas at sites such as retroperitoneum where the tumor can grow for a long time potentially becoming atypical before the patient seeks medical attention. Mechanisms other than HMGI-C expression is required for any progression from lipoma to ALT. No adipocytic tumors develop the clinicopathological features of malignancy. Both MDM2 and CDK4 were absent in all benign lipomas that helps to increase the diagnostic accuracy. Also, the fusion gene transcripts promotes chondrogenesis but 96% of cases of lipoma with fusion gene did not contain bone or cartilage. This suggests that fusion genes are not essential factors for the differentiation of adipocytes towards bone or cartilage. HMGI-C or HMGA2 are regulators which stimulate the common pathway leading to the growth of benign mesenchymal tumors. The development of liposarcoma from a lipoma is very rare and no evidence found.

Abbreviations: ALT – Atypical Lipomatous Tumor, MDM2

– Murine double minute 2 homolog, CDK4 – Cyclin dependent kinase 4, HMGI-C – High mobility group protein, SAS - Sarcoma amplified sequence, GLI –Glioblastoma, CHOP - C/EBP homologous protein, LPP – LIM Domain Containing Preferred Translocation Partner In Lipoma, NFIB – Nuclear factor I B, Gd-DTPA – gadolinium DTPA (diethylenetriamine penta-acetic acid), p53 – protein 53, pRb - retinoblastoma protein

Conflict of interest: Author's declare that there is no conflict of interest.

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