

Cytogenetic study on some common bone tumours

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Abstract:

This study aimed to detect the consistent chromosomal abnormalities of each type of common bone tumours . Thirty bone tumors specimens were processed for direct cytogenetic preparation , only (9 cases) showed success results for chromosomal preparation by banding technique , the results of cytogenetic study were

1- Osteosarcoma (4) cases revealed multiple numerical and structural changes with complex karyotype and pronounced cell to cell variation . chromosome 17 was the most frequent involved in these chromosomal alteration . Also loss or structural changes of chromosome 13 was found in (2) cases of osteosarcoma loss or gain of sex chromosome were detected in these cases , loss of Y chromosome in (2) cases ; loss of X chromosome in (1) case and gain of X chromosome in another case .

2- Osteochondroma : revealed the simple numerical change with no structural change in one case .

3- Chondroblastoma : in this tumor structural and numerical abnormalities of chromosome 5 .

4- Chondrosarcoma : showed chromosomal aberration with multiple numerical and structural changes in chromosome (1) was of interest and monosomy 18 was reported in one case .

5- Giant cell tumors : It showed a complex changes and the range of chromosomal number was 50 – 58 with the characteristic telomeric fusion in malignant cases while simple numerical change only in benign giant cell tumor .

Conclusion

Cytogenetic study of both benign and malignant bone tumors have revealed abnormalities in the number and / or structures of chromosomes X, Y , 1,5,6,11 , 13,17,18 and complex chromosomal changes in malignant types of bone tumors .

key word: cytogenetic study on common bone tumors .

Introduction:

Cancer is a disorder of cell growth , originated from a cellular aberration lead to a symmetrical mitotic figures and loss of defined tissue mass , the cancer cytogenetic is both clinically and methodology useful and a means of obtaining research knowledge on basic tumor biology (1) . To develop a new approach to the diagnostic problems , cytogenetic and molecular genetic adding a new dimension to the formulation of diagnosis because cytogenetic finding of bone and soft tissue tumor provide resolution . of cellular origin (2) . the cytogenetic of both benign and malignant bone tumor have revealed abnormalities in the number and / or structure of many chromosomes . A highly malignant neoplasms appear to have more complete changes than low malignant , benign tumors (3) . Tumor specific chromosomal

abnormalities have been identified in several histologic subtypes of benign and malignant bone tumors . These abnormalities have proven to be useful diagnostically. Characterization of recurrent chromosomal abnormalities also have provided direction for a molecular investigation of pathologically important genes (4) . However the number of cytogenetic studies on bone tumor are few , for this reason this study aimed to : identify both numerical and structural chromosomal changes through cytogenetic analysis of each type of most common bone tumor .

Materials and Methods:

Tumor Specimens :-

Fresh bone tumor specimens were taken from patients , brought to the laboratory , immediately after resection in cold sterile serum free RPMI – 1640 , the tumor samples was placed in sterile disposable petri dishes and examined carefully , any bloody necrotic – tissue and normal tissue

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were trimmed away . The tumor sample was then washed twice by Serum – free RPMI – 1640 medium with antibiotic (5) .

Tumour Disaggregation

Mechanical disaggregation was applied to the tumour samples. The tumour samples was placed in a sterile disposable petri dish containing a small volume (2-3 ml) of RPMI-1640 enriched with 20% human plasma, and antibiotics. The specimen was then cut and minced finely by two opposing scalples, the degree of disaggregation was considered good when all the fragments passed through the tips of 10 ml pipette. The mixture was pipetted vigorously several times to release more free cells (5).

Direct Cytogenetic Preparation

Cell suspension (2-3 ml) was seeded into 25 cm³ flask with 5 ml growth medium containing 0.1 ml colcemid and incubated at 37C° for two hours. Then the suspension transferred into a centrifuge tube and centrifuged at 1500 rpm for 10 minutes. The supernatant was discarded by pipetting off media, leaving as little medium as possible over the cell pellet(5).

Hypotonic Treatment

The cells were resuspended in 2ml prewarmed 0.075 Kcl at 37C° with continuous shaking, then the volume was made up to 8-10 ml by adding more prewarmed 0.075 KC1 gradually with constant shaking. Then the culture tube were incubated in water bath for 30 minutes at 37C°. The cell suspension then was collected by centrifugation at 1500 rpm for 10 minutes, the supernatant was discarded by pipetting off leaving as little supernatant as possible over the cell pellet.

Fixation

The pellet was gently mixed with 5 drops of freshly made fixative solution (methanol and glacial acetic acid in the ratio of 3 : 1 v/v). Cell suspension was then left for 30 minutes at room temperature and centrifuged at 1500 rpm for 10 minutes. The fixative was removed, and an other 5 ml of freshly made fixative was added as above, and the cells were collected by centrifugation. Fixative was changed three times, and after the final change the cells were resuspended

in 3 ml of freshly made fixative and stored at - 20 for at least 2 hrs before spreading on slides(5).

Slide Making

The cell suspension was removed from the freezer and centrifuged at 1500 rpm for 10 minutes, the supernatant was discarded and cells resuspended in appropriate amount of freshly made fixative to make the suspension thin cloudy. With a pasteur pipette 2-3 drops of cell suspension were dropped from 30 cm on a wet, chilled, grease-free slide. The excess solution was removed from slides by filter paper (5).

Staining

Slides were stained with freshly made Giemsa stain (1 part Giemsa stain to 4 parts sorenson’s buffer) for 2-3 minutes. Slides then washed by sorenson’s buffer, allowed to air dry at room temperature and the excess buffer removed from slide by filter paper(5).

Giemsa - Banding (G - banding)

Slides were left for one day at room temperature before undergoing G-banding. Destaining was performed by rinsing slides with fixative and left to dry. Slides then incubated at 80C° for one hr. before processed to trypsinization. Trypsin solution for banding process was spread over slides for 12-15 seconds at room temperature. Slides were then washed by phosphate buffered saline, stained by freshly made Giemsa stain (1 Part Giemsa stain and 4 parts Sorenson’s buffer) for 2 minutes and washed with Sorenson’s buffer. The excess buffer was removed from slides by filter paper. Karyotypes were described according to the international system for human cytogenetic nomenclature (5) .

Cytogetic Study

Cytogenetic analysis have been carried out on 30 benign and malignant bone tumours. Analyzable metaphases were obtained in only nine cases (30%), In four cases metaphases with short, fuzzy chromosomes could be counted but not analyzed (13.3%). unspread metaphases, chromosomes could not be counted were detected in five cases (16.6%). Cytogenetic analysis of the remaining 12 bone tumours specimens were unsuccessful, So no metaphases obtained in 12 cases (40%), as shown in table(1).

Table 1 : the number of fresh bone tumours samples received ; and the results obtained from them .

Number of cases	Results obtained
12	No metaphases were obtained
5	Unspread metaphases , chromosome could not be counted
4	Metaphases with short , fuzzy chromosome could be counted but not analyzed
9	Metaphases with chromosome good enough for analysis

1- Bone forming tumors :- malignant Bone Forming tumors

Osteogenic sarcoma

Analyzable metaphases were obtained in all osteosarcoma

specimens but in case No.1 there was increased in chromosome fragility , and poor banding quality which complicate the analysis of this specimen

Case No 2 : 11 years old male , this case diagnosed as osteo-

sarcoma , grade III , primary tumour .

Cytogenetic analysis

Thirteen metaphases were fully analyzed from the biopsy, three of them were karyotypically normal . Clonal chromosomal abnormalities were detected in the other cells, all these cells were near diploid. The range of chromosome number in this case was 58-65, the numerical and structural changes was:-

59, -x, -y, +2, +3, +7, +12,+13, +13, +13, -15, -17, + add (19) (q13), +20, +20 +20, del(21) (q23), + mar 1, + mar 2,+ mar3, + mar4, + mar 5 (Fig-1)

Case No 3 : 9 years old male , diagnosed as osteosarcoma , grade IV , primary tumour .

Cytogenetic analysis

Two different samples from the operation, specimen were investigated. The first one was excisional biopsy and after 2 weeks another specimen was taken from the amputated limb. Eight metaphases were obtained from the first sample, and six metaphases from the second sample. Complex chromosomal complements were seen in these two specimens and increased chromosomal fragility was present in the form of gaps, breaks, and triradial figures. The range of chromosome number in this case was 53-60, and the mode number was 55.

The analyzable metaphases showed a complex karyotype

55, xxy, +1, +1, -4, +6, +7, +11, +12, +add (20) (q 13), + mar 1 + mar 2 , + mar 3

Case No 4: 15 years old male, diagnosed as osteogenic sarcoma, grade III, primary tumour .

Cytogenetic analysis

Seven metaphases were obtained from the specimen. The range of chromosome number was 60-65, and the mode number was 63. the representative cell karyotype was :-

63X, -y, +2, +3, -5,+5,+5,+6,+10, +11, +12, +12,-13, +14, +14, +15, +17, -19, +20, + add (20) (p 13), + add (20) (p 13), + add (20) (p13), + 21, + mar 1 (Fig. 2)

Case No.5 : 22 years old female, diagnosed estrogenic sarcoma , grade IV , recurrence tumour .

Cytogenetic analysis

The number of counted and analyzable cells were 14. The range of chromosome number was 65-78, and the mode number was 76, all numerical and structural changes were:-76x, -x, +1, +3, +3, +4, +4, +5, +5, + del(6) (q23), - 7 , + 8 , + 1 0 , - 1 1 , add(13) (p 13), add(13) (p 13), +add (13) (p 13), + i(13q), + t(13,x) (p 13, p 11) , +14, add(17) (p 12), + add(17) (p 12), -18, +20, + 20 , +20, add(20) .(p13), +22, +22, +22. (Fig. 3)

2. Cartilage forming tumours

A- Benign

1- Osteochondroma

Case No 7 : Nine years old male diagnosed as osteochondroma , primary tumour .

Cytogenetic analysis Only eight analyzable metaphases were karyotyped from this case. The chromosome number range between 46-48, and the mode number was 46.

No structural changes were detected in this case .

2. chondroblastoma .

Case No.13: Fifteen years old male, diagnosed as chondro-

blastoma, primary tumour.

Cytogenetic analysis :-

Twenty two metaphases were analyzed from the biopsy, eight of the 22 cells were karyotypically normal. The other cells showed range chromosome number 47-48 and the mode number was 47. The cytogenetic -analysis of chondroblastoma in this study revealed the following chromosomal complements:

47 Xy , +5, t(5; 5) (p10; q10) .

B- Malignant cartilagenous Tumor (chondrosarcoma)

Case No 14 : Twenty one years old female, diagnosed as chondrosarcoma, grade III, primary tumour.

Cytogenetic analysis

In 5 of the 8 analyzed metaphases, the karyotype 56 xx, +2, +t(1, 3) (q36; p26), add(4) (p 16), + i(5p), +7, +11, + 1 3 , -1 5 , +add(19) (q 13), +20, mar 1, mar 2, mar3. (Fig. 4). observed and the remaining cells had a normal karyotype. The range of chromosome number in this case was 56-60 and the mode number was 56.

Case No. 15: Forty two years old male, chondrosarcoma, grade IV, primary tumour.

Cytogenetic analysis

Ten mitosis with abnormal male karyotype were noted. The chromosomal number range was 67-68 and the mode number was 65. The aberration were loss of chromosome x, 9, 10. 18 and gain of chromosome 5, 5, 7, 7, 8, 12, 14, 14, 17, 19, 21,22 and 3 markers. Thus the tumour karyotype was 65 x, -x, +5, +5, +add(5) (p 15), del(6) (q24), + 7 , + 7 , - 8 , - 9 , - 1 0 , + 1 1 , +add(11) (q25), +12, +12, add(13) (p13), t(13; x) (p13: pi 11),+14,+14, \ i(16q), + add (1 6) (p 13), +17, -18, +19, +add(20) (p 13), +21. +22, + mar1, ma2 + mar3 (Fig 5) .

3-Giant Cell Tumour (Osteoclastoma)

Case No. 16: Twenty five years old male , dignosed as benign giant cell tumour .

Cytogenetic analysis

Only 9 metaphase were analyses from the biopsy the range of chromosome number was 46-47 , and the mode number was 47 .Four of these metaphases were karyotypically normal. Abnormal clone was detected in the remaining cells and consisted of 47 x y + 7 (Fig . 6)

Case NO 17 : 28 years old female , diagnosed as benign giant cell tumour , primary tumour .

Cytogenetic analysis :

The counted and analyzable metaphases was 28 metaphases , the range of chromosome number was 45-48. The mode number was 45. The cytogenetic analysis of this case revealed the following karyotypes 45xx , - 111 .

Case No . 18 : Twenty one years old female , diagnosed as a malignant giant cell tumour , grade III , primary tumour .

- Cytogenetic analysis

Fourteen metaphases obtained in this case. The chromosome number range was 50-58 and the mode number was 54. (Fig. 7)

All metaphases showed a complex karyotype which was: 54 x, -x, +1, +5, del (6) (q27), +7, +10, +12, add(13) (p 12), add(17) (q 13), fus(1 8 , ?) (qter , ?), +19, add(20) (p 13), add (20) (p13) .

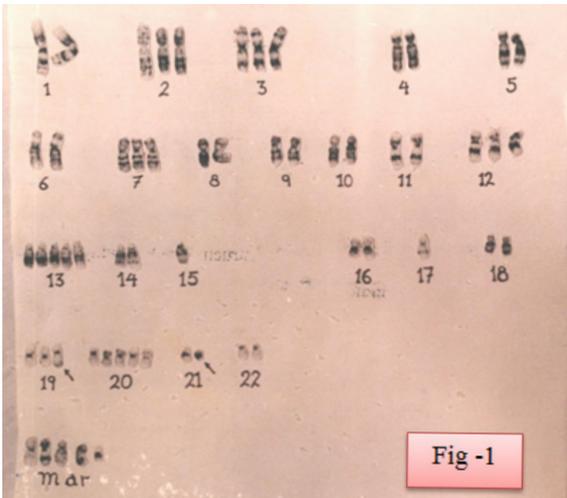


Fig 1: Karyotype form case No.2 A Structural abnormality indicated by arrow

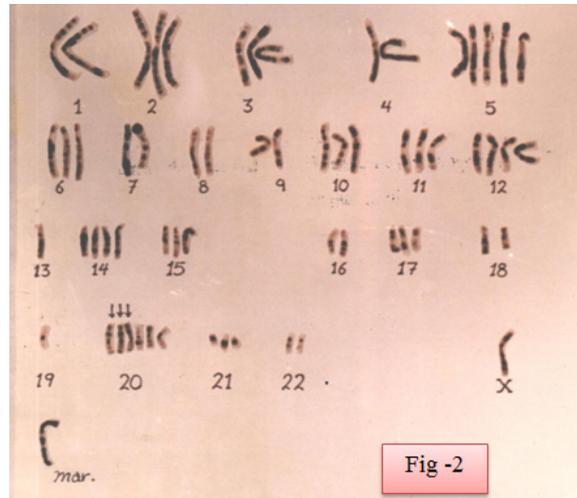


Fig 2: Karyotype form case No.4 A Structural abnormality indicated by arrow

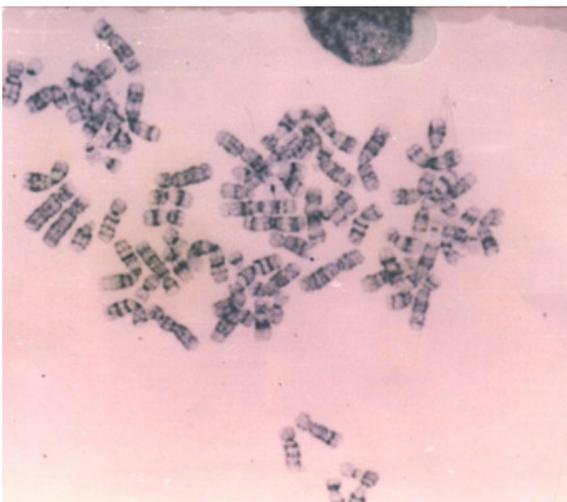


Fig 3 : Metaphase cell from case No . 5 indicate the complex chromosome abnormalities

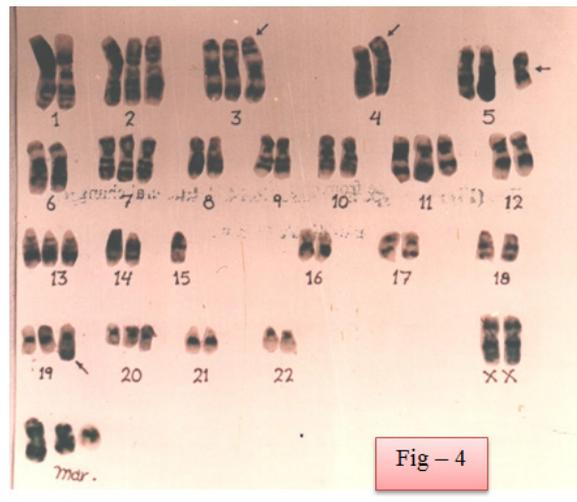


Fig 4 : Karyotype form case No.14 A Structural abnormality indicated by arrow

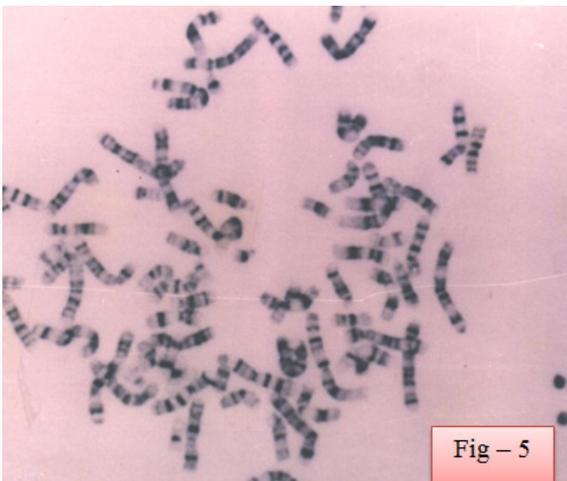


Fig5: Metaphase from case No.15 showing complex chromosomal change including multiple numerical and structural changes

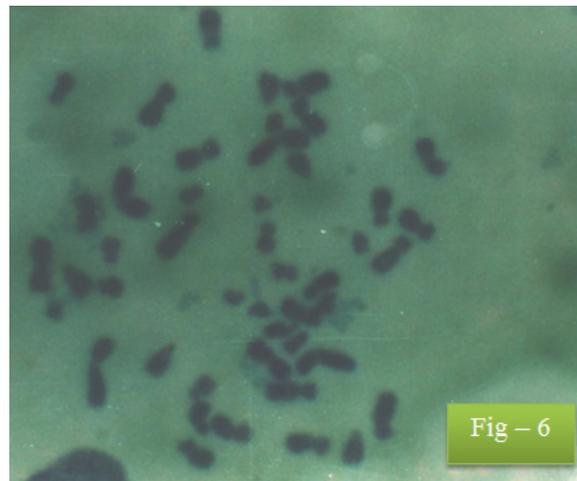


Fig 6 : Metaphase from case No.16 showing simple numerical change

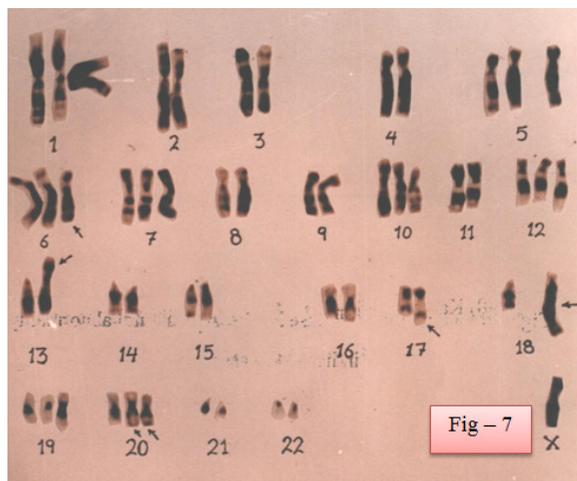


Fig 7 : Karyotype form case No.18 A Structural abnormality indicated by arrow

Discussion:

1- Bone Forming Tumours

Malignant Bone Forming Tumour (Osteosarcoma)

cytogenetic analysis of four cases of osteosarcoma revealed that the chromosomal bands or regions:- 6q32, 13p 13, 17p 12-13, 20p 13, 21q23, were involved in structural abnormalities in all cases.

Numerical changes were represented by gains of whole chromosomes more than losses, the most frequent chromosomal gains were + 1, +2, +3, +5, +6, +7, +8, +10, +11, +12, +13, +14, +15, +20 and the most common losses were, -x, -y, -4, -11, -13, -17, -19 .

The frequent loss of chromosome 17 and high incidence of structural alteration of 17p 12-13 were of interest because other type of solid tumour known to be characterized by abnormalities of 17p such as colorectal cancer (6). Mutations had been detected in Tp53 (a tumour suppressor gene) which was localized to 17p 13. The result was consistent with previous observation of frequent loss or structural alteration of chromosome 17 in sporadic osteosarcoma (7, 3 , 8). Tp53 deactivation contributed to genetic instability which was responsible for the cytogenetic complexity and heterogeneity in high-grade osteosarcoma. 'Genetic instability was believed to accelerate acquisition of mutation in preneoplastic and neoplastic cells, and the high frequency of apparent genetic instability in high-grade osteosarcoma suggested that multiple genetic aberrations were required for neoplastic progression in these tumour (7).

Germline mutation ofTp53 was a feature of Li-fraumeni syndrome, an autosomal dominant disorder predisposing affected individuals to an increased risk of developing osteosarcoma as well as other types of malignancies (9). Corresponding loss of chromosome 13 and/or structural alteration of these chromosome were frequent cytogenetically in this study. Such abnormalities were reported previously by (10), (7), (3). Other suppressor gene, the RBI (retinoblastoma) gene was localized to 13q 14, loss or mutation of these gene was common in sporadic osteosarcoma (3). Moreover, patients with hereditary retino-

blastoma and germline mutation of RBI frequently developed osteosarcoma, and DNA alteration of RBI had been show to correlate with a poor prognosis in sporadic osteosarcoma (11). Other potentially significant, the partial loss of chromosome 6, included 6q. Comparison with previously reported karyotypes also supported this finding, and the previous reports describing a structural abnormalities of 6q resulting in partial loss of the long arm in osteosarcoma (12 , 3). Abnormality of the long arm of chromosome 6 also reported in colorectal cancer (6). Also rearrangement or deletion of 6q was also reported in malignant human salivary gland tumours (13), and it had been proposed that 6q putative tumour suppressor genes were involved in malignant melanoma and ovarian carcinoma (3) . Loss or gain of sex chromosomes were observed in these cases of osteosarcoma , in the first case loss of x and y chromosome , gain of chromosome x in the second case, loss of y in the third case, and loss of x in the last case. However, missing y chromosome was seen previously in malignant cells but not in normal cells found in three cases of non-Hodgkin's lymphoma, suggesting that the loss was correlated with the neoplastic process (14). Also y chromosome loss was reported in colorectal cancer cell (6).

Marker chromosomes appeared as one of the most important feature of osteosarcoma karyotype, because every case possessed at least one marker chromosome. These results confirmed previous reports of presence of high percentage of marker chromosomes in osteosarcoma (7 , 3)

In general the majority of osteosarcoma characterized by complex chromosomal abnormalities with pronounced cell-to-cell variation or heterogeneity. The same phenomenon was observed in which extreme cytogenetic complexity was detected in high grade osteosarcoma(15, 10 , 11, 7, 3).

2- Cartilage Forming Tumours

A- Benign

1- Osteochondroma

Cytogenetic an analysis of one case revealed the presence of simple numerical changes and no structural changes was detected in this case, this result was in agreement with previous

observation in which simple chromosomal complements were found in benign and low grade bone malignancies (16) .

2- Chondroblastoma

Cytogenetic analysis of chondroblastoma revealed the involvement of chromosome 5 abnormality, gain of chromosome 5 and t(5, 5) (p10; q10) were detected in this case, these results almost compatible with study of Swart(4) , who reported that cytogenetic analysis of benign and malignant chondroblastoma characterized by preferential involvement of chromosome 5 and 8. However chromosome 8 abnormality was not detected in this case .

B- Malignant cartilage Forming Tumour (Chondrosarcoma)

Two cases of chondrosarcoma were analyzed cytogenetically . The Karyotypes observed in chondrosarcoma were complex . These findings were consistent with previous observation of complexity of clonal aberration in high grade chondrosarcoma (13).

The obtained results were shown that the chromosomal bands 1q36 , 3p36 . 4p16 . 5p15 , 19q13 , 6q24 , 11q25 , 13p12 , 16q13 , 20p13 were involved in structural-abnormalities in two cases.

Examination of these data and previously reported karyotypes revealed that chromosomal band 1q was the most frequent structural abnormality in chondrosarcoma (17)

Gains and losses of whole chromosomes were frequent in chondrosarcoma . The most frequent numerical gain was +2, +5, +7, +8, +11, +12, +13,+14, +17, +19, +20, +22, and the most common losses were, -x, -9, -10,-15, and -18. Monosomy 18 was detected in one case. This phenomenon was also reported in previous most frequent change in high grade chondrosarcoma (13). The modal chromosome number was near diploid to near tetraploid . (17) had revealed that the modal chromosome number of chondrosarcoma ranged also from near diploid to near tetraploid. The majority of karyotypes observed in osteosarcoma and chondrosarcoma were complex, and the complexity of clonal aberrations correlated with the

grade of malignancy as the osteosarcoma or chondrosarcoma of high grade demonstrated chaotic abnormalities. The chaotic nature of the aberrations implicated the evolution of several different clones and thus advanced malignant transformation (13) .

3- Giant Cell Tumour (Osteoclastoma)

Three cases of giant cell tumour were successfully analyzed cytogenetically , obtained results were showed that telomeric fusion was observed in one case (malignant giant cell tumour grade III). Telomeric fusion was the most prominent of giant cell tumour (18,19,20). In addition to being particularly prominent in giant cell tumour , telomeric fusion was also common in malignant fibrous histiocytoma (21). Giant cell tumour and fibrous histiocytoma of bone radiographically appeared to originate in similar location (metaphyseal / epiphyseal) of long bones, and histologically both were characterized by the presence of giant cells most frequently embedded in a background of mononuclear cells of spindle shape, the exact histopathogenesis of these two neoplasms was unknown, although most investigators favor a fibrohistiocytic origin of both (18). The observation therefore of similar cytogenetic findings in giant cell tumour and malignant fibrous histiocytoma lends further support to a close relationship between these two neoplasms. The chromosomal gains included +1, +5, +7, +10, +12, +19 and losses of chromosome x and 11. Predominant involvement of chromosome 11 (Complete loss , telomeric fusion, and structural rearrangement) were observed in previous study (18) One solid tumour known to be characterized by abnormality of chromosome 11 was Wilms tumour, neoplasm of kidney primarily affecting children and histologically composed of primitive or abortive glomeruli and tubules. Wilm's tumour may occur in a hereditary or non-hereditary form. A chromosomal abnormalities of chromosome11, was noted in almost patients with the hereditary form (22).

Regarding the identification of histomorphological features of these all bone, cartilage forming tumors and giant cell tumors were similar finding (23,24,25,26,27,28,29,30).

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دراسة وراثية خلوية لبعض أورام العظام الشائعة في الإنسان

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2 كلية الطب البيطري/ جامعة بغداد

الخلاصة:

تضمنت هذه الدراسة اجراء دراسة وراثية خلوية لمرضى اورام العظام وشملت الدراسة ما يلي :-

1 - دراسة وراثية خلوية تضمنت تحديد التغيرات الكروموسومية لكل نوع من انواع اورام العظام التي تم الحصول عليها وتحديد اي التغيرات الكروموسومية اكثر تكرارا، ومحاولة ايجاد العلاقة بين التغيرات الكروموسومية للخلية السرطانية وحدة المرض .

2 - اما نتائج التحليل الكروموسومي التي تمت بنجاح في 9 حالات فقط باستخدام طريقة التحضير المباشر فكانت كالآتي :

1 - الغرن العظمي :- ان التغيرات الكروموسومية العددية والتركيبية لخلايا هذا الورم كانت كثيرة وان الهيئة الكروموسومية للغرن العظمي تتميز بكونها معقدة ومختلفة من خلية الى اخرى وكانت اكثر الكروموسومات تعرضا للتغيير العددي او التركيبي هو كروموسوم 17 . اما كروموسوم 13 فقط تعرض للتغيير العددي والتركيبية في حالتين . لقد اوضحت النتائج ان الكروموسومات الجنسية في حالة الغرن العظمي اكثر عرضة للفقدان حيث فقد كروموسوم Y في حالتين وكروموسوم X في حالة واحدة واكتسب كروموسوم X في حالة اخرى .

2 - الورم العظمي الغضروفي :- اظهرت التحليلات الكروموسومية لحالة واحدة لورم عظمي غضروفي تغيير عددي بسيط وعدم وجود أي تغيير تركيبية لاي كروموسوم .

3 - ورم بانية الغضروف الحميد :- في هذا النوع من اورام العظام الحميدة وجد ان كروموسوم 5 هو الكروموسوم الاكثر تعرضا للتغيير العددي والتركيبية .

4 - الغرن الغضروفي :- التحليل الوراثي الخلوي للغرن الغضروفي اوضحت بان التغيرات العددية والتركيبية لخلايا الغرن الغضروفي متعددة ومعقدة وان الهيئة الكروموسومية تزداد تعقيدا كلما ازدادت درجة المرض كذلك فان التغيير التركيبي لكروموسوم (1) هو من العلامات المميزة لهذا الورم هذا بالإضافة الى فقدان كروموسوم 18 الذي سجل في حالة واحدة من هاتين الحالتين .

5- سرطان الخلية العملاقة في العظم :- اظهرت نتائج التحليل الكروموسومي لخلايا سرطان الخلية العملاقة الخبيث بان عدد الكروموسومات يتراوح ما بين 50 – 58 وان هذا الورم يتميز بهيئة كروموسومية معقدة وان الصفة المميزة ولهذا النوع من اورام العظام هو وجود الالتحام النهائي لبعض الكروموسومات . اما سرطان الخلية العملاقة الحميد فقد تميز بتغيير عددي بسيط وعدم وجود تغيرات تركيبية تذكر .