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Cytogenetic Analysis of Hepatoblastoma: Hypothesis of Cytogenetic Evolution in Such Tumors and Results of a Multicentric Study

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ABSTRACT: *Hepatoblastoma is a rare pediatric malignant tumor of the liver. Previous cytogenetic reports are sporadic. We karyotyped nine consecutive hepatoblastomas from the Italian centers participating in a multicentric study on hepatic tumors (SIOPEL 1). Six cases showed abnormal karyotypes. The most common abnormalities were trisomies of chromosomes 2 and 20. Four cases showed abnormalities of chromosome 1. On the basis of findings, we speculate the possibility of a cytogenetic evolutive pattern of hepatoblastomas.* © *Elsevier Science Inc., 1998*

INTRODUCTION

Hepatoblastoma is a rare malignant tumor, though it is the most frequently found liver tumor in pediatric patients, accounting for more than 25% of all pediatric hepatic tumors and for nearly 50% of malignant liver neoplasms in this age group. Hepatoblastoma occurs more frequently in very young children (68% of the tumors are detected in the first 24 months of life and 88% in children younger than 5 years of age) [1]. A number of associated conditions are present in 5% of the cases [2]. Similarities with other embryonic tumors have been found: hepatoblastomas occur in association with Beckwith-Wiedemann syndrome, and there is a report of the synchronous occurrence of Wilms tumor and hepatoblastoma [3]. The loss of heterozygosity for a recessive allele on 11p13 and p15.5, described in Wilms tumor, has also been observed in biopsy tissue from hepatoblastomas and in explants in nude mice [4]. Histologically, the tumor can be classified in a variety of patterns, but two major types have been described: (1) pure epithelial type with four different subtypes and (2) mixed epithelial-mesenchymal type [5]. The effect on prognosis of the different histologic patterns is still under investigation.

Abnormal karyotypes have so far been reported in only a small number of hepatoblastomas, partly owing to the rarity of these neoplasms. Trisomies of chromosomes 20 and 2 are the most frequent chromosome aberrations, occasionally described as the sole abnormality [6].

We report here on the cytogenetic results of nine consecutive hepatoblastomas. A possible cytogenetic evolution of hepatoblastoma neoplastic clones is suggested on the basis of our results.

MATERIALS AND METHODS

Since 1988, a Childhood Liver Tumor Tissue Storage program has been implemented in Italy for the participants in the Italian Childhood Liver Tumor Study Group of the International Society of Pediatric Oncology for Liver Epithelial Tumors, SIOPEL 1 clinical trial. The aim of this program is to make biological material derived from hepatic cancer patients available for biological studies and basic research projects. All histologic specimens are centrally reviewed by an expert to confirm the diagnosis. To facilitate the centralized handling of the material, a kit for shipping biological material is sent to all the participating centers. The kit containing the tissue specimens is returned to the tissue bank soon after the material has been sampled, using an overnight express mailing service. The tissue bank is located in the Hemato-Oncology laboratory of the Paediatric Department of Padua University [7].

This report presents findings on specimens obtained at surgery from nine patients with hepatoblastoma and analyzed to detect cytogenetic abnormalities. The patients included six boys and three girls, with a mean age of 14.9

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months (range 2–44 months). All but one of the samples were analyzed at diagnosis, before any chemotherapy was implemented. In one case (no. 5), the tissue was obtained from a relapsing tumor. The histological subtypes, serum levels of α-fetoprotein, patients' follow-up, and other clinical and biological characteristics are given in Table 1.

Cytogenetic Methods

The tissue was sent to the laboratory in RPMI 1640 culture medium, 24 or 48 hours after surgical excision. The tissue was finely minced into 1–2-mm^3 pieces and digested in growth medium containing collagenase II (Sigma) at a concentration of 1 mg/mL for 1–2 hours. After disaggregation, the cells were centrifuged, transferred to a fresh medium, checked for vitality, and cultured in a 5% CO_2 atmosphere at 37°C. The growth medium contained RPMI 1640 (GIBCO) with 15% fetal calf serum, 1% L-glutamine, and 50 ng/mL penicillin/streptomycin. Cells for karyotyping were harvested after short-term culture (1–20 days). Colcemid at a concentration of 0.02 mg/mL was added 18 hours before harvesting, when the cultures appeared to be confluent. Cells collected by trypsinization were treated with a hypotonic solution (0.56% KCl) for 20 minutes at 37°C, fixed in methanol and acetic acid (3:1), and dropped onto clean slides. The chromosomes were banded by the QFQ or GTG methods or both. At least 15 metaphases were analyzed. The karyotypes were described according to the ISCN nomenclature [8].

Fluorescence in situ hybridization (FISH) was performed according to a reported method, when the normal banding techniques were unable to identify complex cytogenetic abnormalities [9].

RESULTS

The histologic review established a diagnosis of embryonal hepatoblastoma in six cases and a diagnosis of fetal hepatoblastoma in three cases. Appropriate metaphases for cytogenetic analysis were obtained from 9 patients. Table 1 shows the cytogenetic results and characteristics of the cultures. All but one of the cases with the cytogenetic anomalies showed a trisomy 20 associated with other structural or numerical abnormalities or both. Trisomy 2 was detected in two cases, and one case presented with a partial trisomy of chromosome 2, der(2)t(1;2)(q21;q36) (Fig. 1). In three cases, duplication of all or part of the long arm of chromosome 1 was detected; in one of these cases (case 2), FISH painting for chromosome 1 was performed to better define the translocation. A t(1;4)(q21;q32) was detected in another case (Fig. 2); the two cases with a rearrangement of 1q21 also had trisomies of chromosomes 2, 7, 8, 19, and 20. Five of six tumors had hyperdiploid karyotypes. Only one case presented with a hypodiploid clone with a der(12)t(12;15)(q24;q13).

In one case (case 6), 16 normal diploid metaphase cells were found to coexist with the abnormal clone. Only diploid metaphase cells were observed in six cases.

DISCUSSION

Cytogenetic analysis has proved useful in determining underlying genetic changes, enabling the identification of genetic areas that warrant further molecular biological analysis. It also provides important information for the diagnosis and prognosis of cancer [10].

To date, detailed karyotypic findings have been described in a few hepatoblastomas [11–22], and no specific cytogenetic abnormalities have been identified in these neoplasms, partly owing to their rarity (Table 2). This report describes the results of cytogenetic analysis performed on what is, to our knowledge, the largest series of hepatoblastomas studied so far.

A trisomy of chromosome 20 was detected in five of the six cases with an abnormal karyotype in our series; this is the most frequent cytogenetic abnormality reported. Including our cases, an extra copy of chromosome 20 has been found in 17/28 cases of published hepatoblastomas. In the majority of

Table 1 Clinical, biological, and cytogenetic features of patients

Patient no.	Age (months)	Tumor location	Stage	Histology	α-Fetoprotein (μg/L)	Follow-up (months)	Culture period (days)	Karyotype [no. of cells]
1	15	Right lobe	III	Fetal	27,000	Alive, 24	7	46,XY[30]
2	44	Right lobe	III	Embryonic	61,000	Alive with disease, 21	1	50,XY,add(1)(p32),+2,+6,add(12q),+20,add(22q)[40]
3	8	Right, left lobe	IV	Embryonic	447	Alive, 23	20	53,XY,+der(2)t(1;2)(q21;q36),+7,+8,+8,+19,+20,+21[15]
4	6	Right, left lobe	IV	Embryonic	Normal	Dead, 2	1	46,XX[30]
5	33	Right lobe	III	Embryonic	190	Dead, 3	7	55,XX,t(1;4)(q21;q32),+2,−4,+ i(6)(p10),+7,+8,+15,+17,+17,+19,+20[20](relapse)
6	2	Left lobe	III	Embryonic	2,100,000	Alive, 48	15	46,XY[16]/50,XY,+8,+16,+20,+22[4]
7	7	Left lobe	III	Embryonic	121	Alive, 51	20	46,XY[20]
8	9	Unknown	II	Fetal	350,000	Alive, 35	1	46,XY,i(1)(q10)[10]/47,idem,+20[20]
9	35	Right, left lobe	III	Fetal	2,078	Alive, 59	7	45,XX,−12,−15,+der(12)t(12;15)(q24;q13)[15]

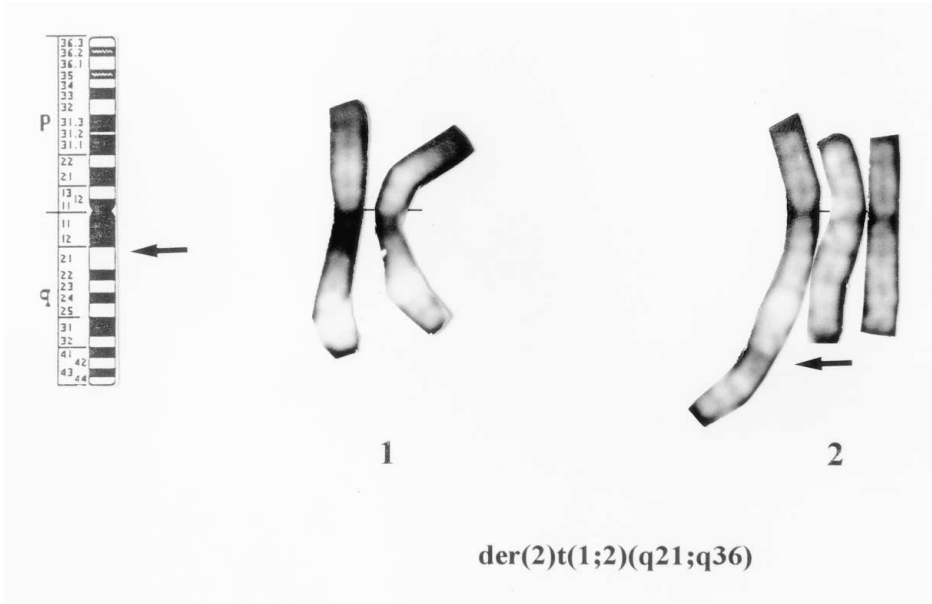


Figure 1 Partial karyotype of case 3 showing the abnormality involving chromosome 1 at band 1q21 and chromosome 2.

these cases, as in ours, trisomy 20 was associated with other abnormalities. In only two cases, trisomy 20 was associated with double minute chromosomes [12], and, in only one case, trisomy 20 was identified as an isolated abnormality. Thus, the authors suggested that, in hepatoblastoma, trisomy 20 could be one of the primary cytogenetic changes associated with tumor development or progression or both [19]. In one of our cases (case 8), we detected two cytogenetic clones, one with an i(1q) and the other with an additional trisomy 20; in this case, the extra chromosome 20 could be associated with clonal evolution of the tumor responsible for the development of different cytogenetic clones or it could be a consequence of the histologic heterogeneity of the hepatoblastoma.

The role of trisomy 20 in the development of these neoplasms may be related to the frequent findings of trisomy 20 in colon adenomas [24]. A significantly increased frequency of hepatoblastoma has been noted in kindred harboring familial adenomatous polyposis. One British study is estimated that 1 in 20 hepatoblastomas is likely to be associated with familial adenomatous polyps at a very early age [25]. Trisomy 20 could constitute the genetic link between the two diseases.

A trisomy of all or part of chromosome 2 was found, together with other abnormalities, in three cases in our series. An additional copy of chromosome 2 or part of its long arm is a frequent finding in hepatoblastoma, reported

Figure 2 Partial karyotype of case 5 with a translocation between chromosomes 1 and 4. The ideogram shows only the breakpoint at band 1q21.

Table 2 Cytogenetic findings in hepatoblastomas

Case no.	Histology	Karyotype	References
1	Epithelial; embryonal	46,XY,−2,der(19)t(4;19),+mar	[11]
2	Mixed mesenchymal-epithelial; fetal	47,XY,+20,dmin	[12]
3	Epithelial; primarily embryonal, foci of fetal areas	47,XY,+20,dmin	[12]
4	Mixed mesenchymal-epithelial; fetal	93,XXXX,+i(8q)/93,XXXX,del(1)(p22),+i(8q)	[21]
5	Mixed mesenchymal-epithelial; fetal and embryonal	47,XX,del(1)(q32.1q32.2),dup(2)(q21q35),+20,dmin/50,XX,+5,+7, +20,+22,del(1),dup(2),i(8q),dmin	[13]
6	Mixed mesenchymal-epithelial; fetal	50,XY,+dic(1)(p12),+2,+8,+20	[13]
7	Mixed mesenchymal-epithelial; fetal	47,XX,dup(2)(q23q35),+20/47,XX,dup(2),dup(6)(p11p24),+20	[13]
8	Mixed mesenchymal-epithelial; fetal and embryonal	54,Y,der(X)t(X;1)(p22;q21),+2,+6,+8,+8,inv(9)(p11q21)+12,+15, +17,+20	[13]
9	Mixed mesenchymal-epithelial; fetal	46,XY,der(4)t(2;4)(q21;q35),t(9;?)(p24;?)/47,XY,der(4),t(9;?),+20	[14]
10	Epithelial; fetal	51,XY,+2,+der(5)t(1;5)(q25;q35),+del(6)(q15),+12,+20	[15]
11	Epithelial; fetal	48,XX,+20,+r/48,XX,+der(2)t(1;2)(q23;p21), inv(5)(q22q35),+20,+r/49,XX,+der(2),inv(5),+20,+r	[15]
12	Epithelial; primarily fetal, foci of embryonal areas	47,XX+2	[16]
13	Mixed mesenchymal-epithelial	47,XX,2q+,t(3;5)(q25;q31),dup(4)(q12q26),+20	[17]
14	Epithelial; fetal and embryonal	46,XY,del(15)(q11q13)	[23]
15	Small-cell undifferetiated	46,XY,t(22;10)(q11;q26)	[18]
16	Not available	46,XY,del(1)(q12)/46,XY	[20]
17	Not available	46,XY,del(10)(p11),del(13)(q31)/46,XY	[20]
18	Not available	49–50,XX,?dirdup(1)(pter→q42::q23→q32::q21→qter),−2, +?dirdup(2)(pter→q33::q21→qter)×2,+6,+7,+20/100–102,XXXX,−1,−1,?dirdup(2)(pter→q33::q21→qter)×2,−4,−5, +6,−7,+9,−12,−16,−19,−19,−21,+16mar/46,XX	[20]
19	Epithelial; fetal and embryonal	46,XY, +20	[19]
20	Epithelial; fetal and embryonal	46,XY,+2	[19]
21	Epithelial; fetal and embryonal	46,XY,del(17)(p12)	[19]
22	Not available	46,XX,der(2)t(2;2)(p25;q21),der(22)t(1;22)(q22;p13)/47,XX,der(2) t(2;2)(p25;q21),+20,der(22)t(1;22)(q22;p13)/47,XX,der(2)t(2;2) (p25;q21),+20	[22]

in 14 cases to date. In two cases of hepatoblastoma, trisomy 2 was the sole anomaly [16, 19]; the authors suggested that this aberration might be a primary change in hepatoblastoma. This hypothesis is not confirmed in our series, however. In fact, in our series, abnormalities of chromosome 2 were always associated with other cytogenetic aberrations. We found no trisomy 2 without an associated trisomy 20, but we did find the opposite situation.

In addition to trisomies of chromosomes 20 and 2, trisomy 8 was another recurrent abnormality, detected in three cases in our series. The polysomy of chromosome 8, often as an isochromosome 8q, has been reported in hepatoblastomas, always associated, as in our cases, with other abnormalities, indicating that they may constitute a secondary abnormality, acting as a putative marker of tumor evolution [13]. In fact, all the cases in our series with trisomy 8 also presented with a trisomy 20, and one had a trisomy 2 associated with trisomies 8 and 20. The polysomy of chromosome 8 is a frequent cytogenetic abnormality of malignant neoplasms and has been associated with tumor progression in several pediatric solid tumors, such as Ewing sarcoma and rhabdomyosarcoma [26, 27]. The clinical meaning of trisomy 8 in hepatoblastoma remains to be established.

In four cases of our series, we found abnormalities of chromosome 1; in three cases, this was a duplication of all or part of the long arm of this chromosome and, in one case, it was a reciprocal translocation involving the breakpoint 1q21.

Numerical or structural abnormalities of chromosome 1 were observed to be a recurrent abnormality in previously described hepatoblastomas. Rearrangements of the long arm of chromosome 1 in the breakpoints from 1q21 to 1q32 in four cases of hepatoblastoma also have been reported [13, 15]. Dressler et al. [20] reported two cases of hepatoblastoma, one with a deletion of nearly all of the long arm of chromosome 1 and the other with a complex rearrangement also involving the long arm of chromosome 1. The rearrangement of 1q21, found in two hepatoblastomas in our series, appears as a recurrent structural abnormality in hepatoblastomas. Recently, 27 cases of hepatoblastoma from the American Pediatric Oncology group were presented at the SIOP meeting [28]; in three cases, a der(4)t(1;4)(q12;q34) was found. The researchers speculated on a role for the breakpoint of 1q12 in the oncogenetic development of the tumors. This breakpoint is very close to 1q21.

In both our cases, the rearrangement of 1q21 was associated with trisomies of chromosomes 2, 7, 8, 19, and 20. Both cases presented with similar clinical features: an aggressive disease. One patient died 3 months after the diagnosis, and the other presented at diagnosis with a stage IV tumor, a low level of α-fetoprotein, and an embryonal histologic type. The two cases with the same 1q21 rearrangement previ-

ously reported also were associated with trisomies of chromosomes 2 and 20 [13, 20]; no clinical data are available.

The frequent finding of a chromosome 1q abnormality in hepatoblastoma suggest a role for chromosome 1 in the carcinogenesis or progression of this type of tumor or both, and the recurrence of 1q21 rearrangements as a secondary anomaly in hepatoblastoma suggests that a putative gene for hepatoblastoma progression could be localized at 1q21 or in its vicinity. Considering the multistep process of carcinogenesis, from the cytogenetic point of view our results indicate that trisomy 20 is the most frequent and probably the primary cytogenetic abnormality in these tumors. Tumor evolution would be associated with an accompanying cytogenetic evolution with the additional abnormalities being in the sequence: trisomies of part or all of chromosomes 2 and 8 and abnormalities of chromosome 1, as a duplication or rearrangements of the long arm. The role of the recurrent rearrangement of 1q21 in hepatoblastoma must be verified; nevertheless, our two cases suggest a possible relation between aggressive disease and these multiple abnormalities. The histologic heterogeneity of hepatoblastoma, which often presents with a mixture of cells of mesenchymal and epithelial origin, could be responsible for clonal karyotypes differing from those commonly found and from the "cytogenetic evolution" that we suggest. This may apply to one case (case 9) in our series, as well as to some cases in the literature.

In one case (case 2), the cytogenetic abnormality involved the breakpoint 1p32. Chromosome 1 abnormalities have been frequently reported in pediatric solid tumors, most often as a rearrangement or deletion of the terminal part of the short arm of the chromosome [29]. A deletion at 1p22 was described in one hepatoblastoma [21]. An association of 1p deletion with aggressive disease was reported in neuroblastoma and was also recently described in a small series of peripheral neuroepithelial tumors [30]. Polysomy and rearrangements of chromosome 1 were reported in hepatocellular carcinoma, another primitive hepatic tumor. Recently, deletions of the short arm of chromosome 1 at breakpoints p22 and p32, were identified in four of five adult patients with primary hepatocellular carcinoma [31]. A role for 1p involvement in hepatocarcinogenesis has been suggested and supported by the demonstration of loss of polymorphic alleles from distal 1p in hepatocellular carcinoma [32]. However, the same authors failed to demonstrate loss of heterozygosity on 1p in the two hepatoblastomas studied [32].

A link between hepatoblastoma and other embryonic tumors has been suggested. The cytogenetic picture seems to strengthen this hypothesis. In fact, chromosome 2q abnormalities have frequently been reported in embryonic rhabdomyosarcoma [33]. Extra copies of chromosome 20 have been observed in congenital fibrosarcoma [34], in Wilms tumor [35], and as the most frequent abnormality in cultured amniotic fluid cells [36]. In one case in our series, we also found a rearrangement of chromosome 2 with a breakpoint at 2q36, the same breakpoint frequently involved in rhabdomyosarcoma.

Only one case in our series presented with a hypodiploid karyotype without the cytogenetic abnormalities that appeared in the other hepatoblastomas of our series and in those previously described. We speculate that this could be a different tumor, at least from a cytogenetic point of view.

The normal karyotypes of three cases in our series probably represent stromal cells rather than tumor cells. All but one of these cases were cultured for at least 1 week. It is always best to set up direct, overnight, 24-hour cultures, because they are the most reliable for growing tumor cells.

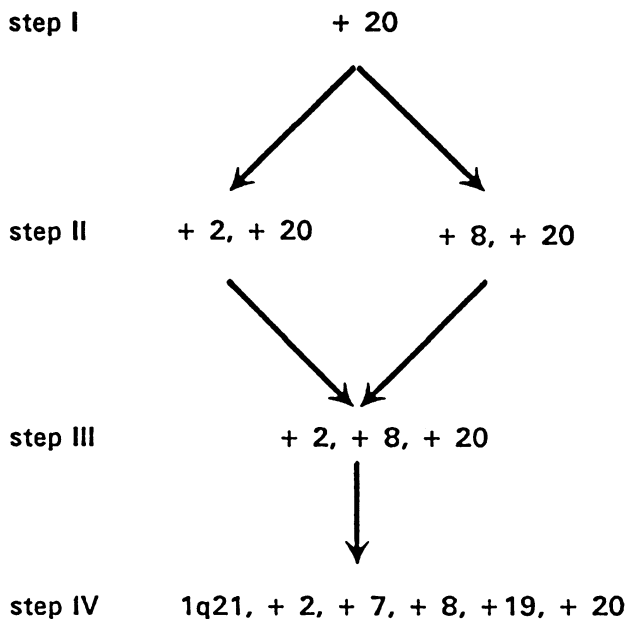
In conclusion, our study demonstrates that cytogenetic analysis can be performed on hepatoblastoma tissue shipped by an ordinary mailing system. This is important for organizing multicentric studies, which are essential to the study of rare tumors such as pediatric hepatoblastomas.

We can confirm that trisomies of chromosomes 2, 8, and 20 are frequent findings in hepatoblastoma, and we also point out the recurrence of trisomies of chromosomes 7 and 19.

The hypothesis of cytogenetic evolution of at least a subgroup of hepatoblastomas emerges from our analysis (Fig. 3): the clonal evolution indicates trisomy 20 as the primary cytogenetic abnormality, with trisomies 2 and 8 coexisting or being alternative abnormalities; rearrangement of the long arm of chromosome 1—namely, at 1q21—seems to be a late-onset abnormality, often associated with trisomies of chromosomes 7 and 19. However, hepatoblastoma is probably a heterogeneous type of tumor, not only histologically, but also cytogenetically. This explains the detection of other cytogenetic abnormalities, such as the isolated trisomy 2, or those found in case 9 of our series.

Further studies are needed to confirm the association of certain cytogenetic abnormalities with hepatoblastoma and to clarify the clinical and biologic meanings of these cytogenetic changes.

Figure 3 Hypothesis of cytogenetic evolution in hepatoblastomas.



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