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FAMILIAL GLIOBLASTOMA

WALTER O. ARRUDA, ROGÉRIO S. CLEMENTE**, RICARDO RAMINA**, ARI A. PEDROZO**, RUI F. PILOTTO***, WALTER PINTO JR. ****, LUIZ F. BLEGGI-TORRES******

SUMMARY - The authors describe a family with three members affected by glioblastoma. The proband patient, a 7 year-old girl, developed a rare complication, a pulmonary metastasis. Chromosomal analysis of her peripheral blood lymphocytes showed a normal karyotype (46, XX), without structural abnormalities. Cytogenetic study of the tumor cells disclosed several abnormalities: 46, XX, 7q- / 46, XX, -2, 4p-, 7p-, +15/ 46, XX. Some aspects about genetics of glial neoplasms are discussed.

KEY WORDS : glioblastoma, chromosomes, cytogenetics, oncogenesis.

Glioblastoma familiar

RESUMO - Os autores descrevem uma família com três membros portadores de glioblastoma. A paciente probanda, uma menina de 7 anos, apresentou metástase pulmonar. A análise cromossômica dos linfócitos periféricos revelou um cariótipo normal (46, XX). Estudo citogenético das células tumorais mostrou várias anormalidades: 46, XX, 7q- / 46, XX, -2, 4p-, 7p-, +15 / 46, XX. Alguns aspectos sobre oncogênese e citogenética das neoplasias gliais são discutidos.

PALAVRAS-CHAVE: glioblastoma, cromossomos, citogenética, oncogênese.

The occurrence of glioblastoma in more than one member of a family is uncommon[4,6,9,12,14,18]. Some cases of familial gliomas are associated with genetic syndromes, such as tuberous sclerosis, neurofibromatosis, von Hippel-Lindau, colonic polyposis (Turcot's syndrome) , and hepatic focal nodular hyperplasia, whereas other cases occur as isolated findings[16,17]. Cytogenetic analyses of the central nervous system (CNS) have revealed some relatively specific chromosomal abnormalities. For example, deletions of chromosome 22 have been frequently observed in meningiomas and in neurofibromatosis type II[16,17]. Neuroblastomas often have deletions of 1p, and when their cells show an amplified oncogene, *N-myc*, a poor clinical outcome can be predicted[23]. Frequent allelic losses of chromosomes 9p, 10, 17p, 19, and 22q are present in some glial tumors[15].

There are few reports of cytogenetic analysis in familial cases[6]. We report a patient in a family with several members having glioblastoma and the cytogenetic findings in this patient.

FAMILY DESCRIPTION

The heredogram is shown in Figure 1. The proband patient (IV-2), a 7 year-old girl, complained of headaches and vomiting since January 1988. At this time, neurological examination disclosed bilateral papilledema, and a CT scan two weeks later showed a left occipital tumor lesion. She underwent surgery, with radical excision of the tumor. Histological examination showed a

*Neurologista, **Neurocirurgião, *****Neuropatologista, Unidade de Ciências Neurológicas, Hospital das Nações, Curitiba; ***Geneticista, Unidade de Genética Médica, Universidade Federal do Paraná; ****Geneticista, Departamento de Genética Médica, UNICAMP. Aceite: 24-outubro-1994.

Dr. Walter Oleschko Arruda - Rua Gonçalves Dias 713 - 80240-340 Curitiba PR - Brasil.

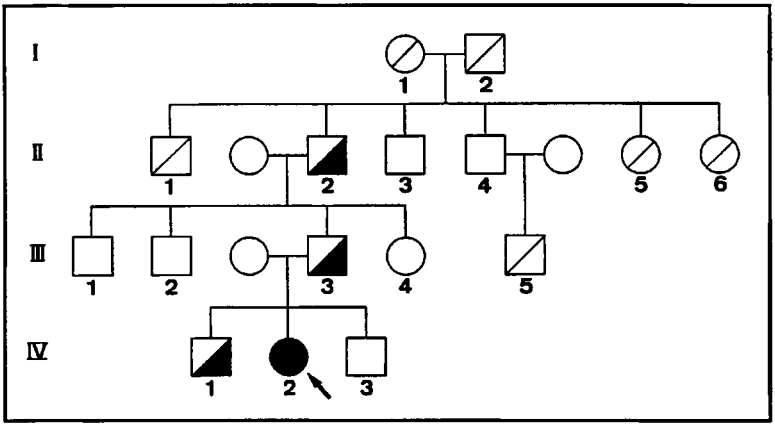

Fig 1. Heredogram of the family. Half shaded symbols, brain tumors, deceased. Arrow, proband patient. Oblique lines, deceased. Roman numerals indicate generations; arabic numerals identify individuals.

Fig 2. Chest-X-ray showing a nodular lesion in the right hemitorax.

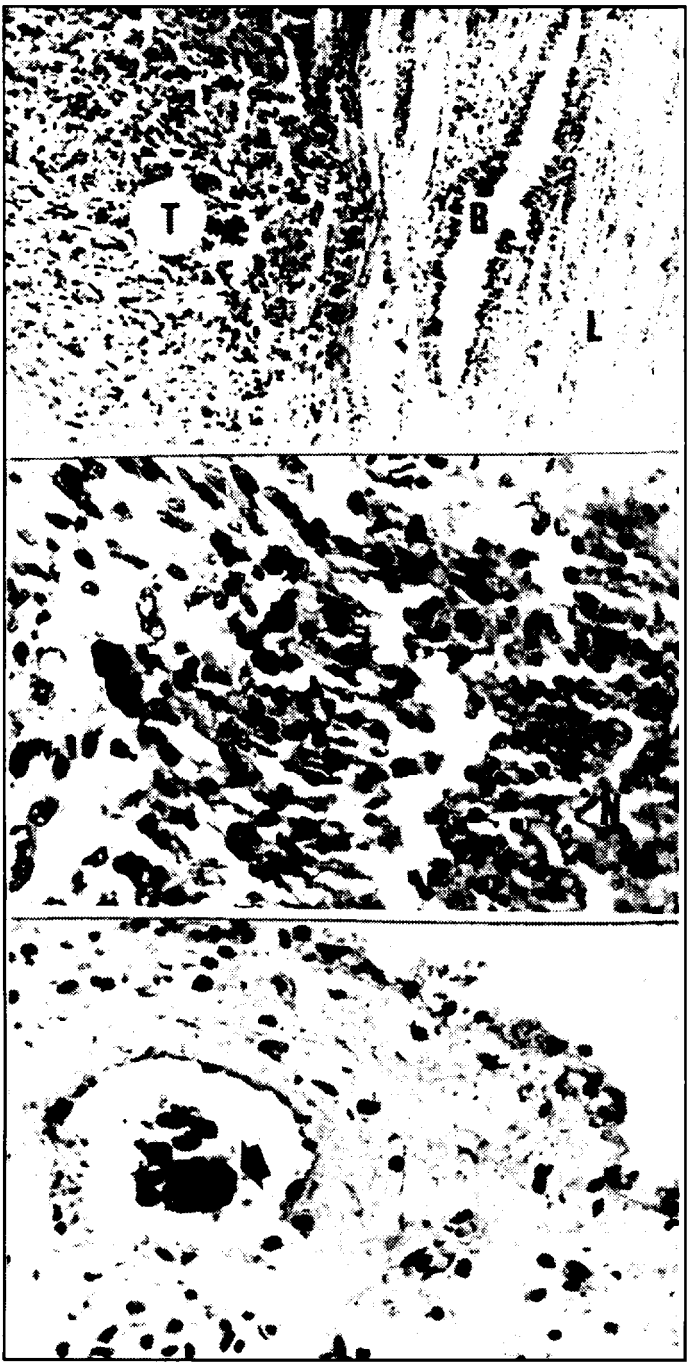

Fig 3.a- Glioblastoma (T) affecting lung tissue (L). Bronchial tree (B) evident. HE x40; b - Tumor cells are pleomorfic and bizarre with foci of necrosis (N). HE x400; c- Immunohistochemistry for GFAP showing intense positivity in tumor cells that are embolizing a lymphatic vessel of the lung (arrow). Avidin/biotin x400.

glioblastoma. The operation was followed by radiotherapy and chemotherapy. In October 1989, a chest X-ray showed a nodular lesion in the right lung (Fig 2). The lesion was totally removed through a thoracotomy. Pathological examination disclosed glioblastoma. Immunohistochemical study of the brain and lung lesions showed positive reaction for GFAP, S-100, and focal reaction to enolase (Fig 3). In December 1989, the cerebral lesion recurred and she had surgery again. The patient died in May 1990 due to neoplastic recurrence. The brother of the proband (IV-1), 7 years-old, had a quite similar clinical picture, and a tumoral lesion was detected in the right frontal lobe. He was operated on in November 1986, followed by radiotherapy, and died in January 1988. Histological examination disclosed glioblastoma. The father of these two children (III-3) had a cerebral tumor lesion diagnosed by CT-scan when he was 30 years-old. He was operated on twice (December 1987 and January 1988), and died in December 1988, after radiotherapy and chemotherapy. The histological diagnosis was also glioblastoma. His father (II-2), the proband's grandfather, died in 1968, with the diagnosis of brain tumor. The histological slides could not be reviewed. Three other members of this family died of malignant neoplasms in other areas: breast, larynx, colon (members II-5, II-6, and III-5, respectively).

CYTOGENETIC STUDY

Cytogenetic study of peripheral blood lymphocytes of the proband patient was normal (46, XX). Culture of tumoral cells with cytogenetic analysis disclosed several structural chromosomal abnormalities: 46, XX, 7q- / 46, XX, -2, 4p-, 7p-, +15 / 46, XX.

COMMENTS

Our patients present some unique features: 1) Other members of the proband's family are affected by the same histological type of neuroepithelial tumor of the CNS, suggesting an autosomal dominant genetic transmission; 2) The peak age incidence of glioblastoma is between 45 and 55 years; it is decidedly rare before 30[17]; and 3) Extraneural metastasis are uncommon with all glioma types; nevertheless, glioblastoma is the most common tumor related with remote metastases, especially to the lungs. Russell and Rubinstein reviewed 116 cases of different types of glioma with extraneural metastases, and glioblastoma was responsible for 41.4% of the cases[17].

Several cytogenetic abnormalities including recurrent site-specific or duplication, chromosomal translocations, deletions and additions are identified in some primary brain tumors[8,20]. Some of these structural chromosome abnormalities have been related with the aberrant expression of a proto-oncogene. Proto-oncogenes encode proteins that regulate cellular replication and cellular differentiation[19,23]. A proto-oncogene may change its function and become a transforming gene, so-called oncogene. The activated oncogene directs the synthesis of qualitatively or quantitatively abnormal proteins that are the real effector of neoplastic transformation. Some examples of oncogenes identified in glioblastoma are *N-myc, c-sis, c-erb-B* and *ros*[19,23]. Proto-oncogenes *c-erb-B* and *c-sis* are respectively mapped to chromosomes 7 and 22[20]. Peptide growth factors are also important for the control of cell growth and differentiation. Proto-oncogene *c-erb-B* encodes the epidermal growth factor receptor (EGFR) and *c-sis* encodes for one of the polypeptides of platelet-derived growth factor (PDGF)[19,20,23]. Interestingly, overexpression of EGFR has been reported in primary brain tumors, including glioblastoma[19]. Furthermore, production of high amounts of PDGF occurs in some glioma cell lines[20,22].

Single structural rearrangement has not been consistently related to specific histological types of human gliomas. It is conceivable that they may be a secondary event in the evolution of the tumor system rather than a primary event[20].

Nevertheless, some relatively specific patterns of chromosome gains and losses have been observed in both astrocytomas and malignant gliomas. Frequent allelic losses of chromosomes 9p, 10, 17p, 19, and 22q were identified[11,15]. Missing sequences of chromosome 10 occur in 53-97% of

glioblastoma cases. Bigner et al[2] detected statistically significant abnormalities of near-diploid tumor such as gains of whole copies of chromosome 7, losses of chromosomes 10, structural abnormalities of 9p and 19q, and the presence of double minutes in 43 cases of glioblastomas. Other numerical changes include losses of chromosomes 22 and sex chromosomes (gonosomes)[1]. A tumor supressor gene located on chromosome 17, *p53,* is frequently affected in many human tumors, including malignant astrocytomas. In fact, *p53* mutations were found in malignant astrocytomas stages but not in low-grade astrocytoma[7]. Fults et al.[7] found loss of heterozygosity on chromosome 10 and *p53* mutation only in patients with glioblastoma (22%), suggesting that these genetic changes may accumulate during astrocytoma progression. Litofsky et al.[13] detected *p53* mutations in 15% of low grade astrocytomas, while this finding occurred in 38% of glioblastomas out of an adult population. However, in pediatric cases, *p53* mutations probably does not play a major role in oncogenesis. Clonal expansion of *p53* mutant cells[21], specific abnormalities on chromosome 17, and chromosome 10 changes[3,10] may influence progression from astrocytoma to glioblastoma. Studies using DNA markers that detect restriction fragment length polymorphism (RFLP) and polymerase chain reaction - single-strand conformation polymorphisms analysis (PCR-SSCP) might be the only way to detect such abnormalities in our case.

We could find only one previous report of two siblings with glioblastoma with chromosome studies[6]. In the first case, numerical and structural abnormalities including translocation between chromosomes 11 and 14, often seen in a tetraploid version of the basic karyotype, were detected. The tumor of the second case contained cells with no numerical and structural abnormalities.

Those findings are quite different from our case. Discrepancy of cytogenetic findings from different reports may be the result of random sampling of the surgical specimen. Furthermore, different regions of the same tumor lesion may or may not show chromosomal abnormalities[20]. Shapiro demonstrated regional karyotypic heterogeneity in glioblastomas resected almost in toto[20]. The observation of different cytogenetic abnormalities that are not observed in all glial tumors may also suggest that tumors with a common histopathological identity may have different molecular genetic profiles.

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