45- YEAR-OLD MALE WITH SYMPTOMATIC MASS IN THE FRONTAL LOBE

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CLINICAL HISTORY, RADIOLOGY

In 1999, at the age of 41 years this man developed focal seizures in his right arm. The neurological examination was otherwise normal. He was in good health and his medical history was devoid of underlying disease. Cranial MRI revealed a homogeneously contrast enhancing lesion with microcalcifications in the left frontal lobe (Figure 1). One year later the patient decided to have stereotactic biopsy. Surgically induced artifacts and small sample size aggravated tumor classification at that time. Differential diagnoses included oligodendroglioma WHO II and diffuse astrocytoma WHO II. In January 2003, at the age of 45 years, the patients developed weakness in his right arm and seizure frequency increased despite medication. Tumor size had considerably increased. Surgery was offered and the patient decided to have the lesion removed through a left frontal craniotomy. The postoperative course, was unremarkable, the weakness of the right arm disappeared.

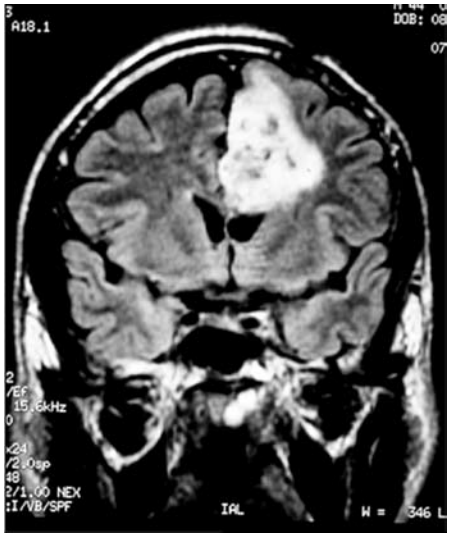

Figure 1.

MICROSCOPIC DESCRIPTION AND IMMUNOHISTOCHEMISTRY

Histology revealed a moderately cellular infiltrative neoplasm and both cortical as well as subcortical involvement. The tumor cells had round and homogenous nuclei. Small groups of tumor cells with clear swollen cytoplasm and well defined plasma membranes were detected in paraffin- embedded sections throughout the tumor (Figure 2A). Other striking morphological features included intratumoral microcalcifications in snap-frozen specimen (Figure 2B), a network of branching capillaries without evidence of microvascular proliferation (Figure 2C), small nucleus- free areas of neuropil (Figure 2D) and perivascular pseudorosette formation of tumor cells (Figure 3A). Immunohistochemically the tumor cells were devoid of GFAP except for occasional entrapped reactive astrocytes (Figure 3B). A strong cytoplasmic expression of neuron specific enolase (Figure 3C) by the tumor cells was noted. Additionally, the nucleus-free "neuropil islands" demonstrated a fine granular expression of synaptophysin (Figure 3D).

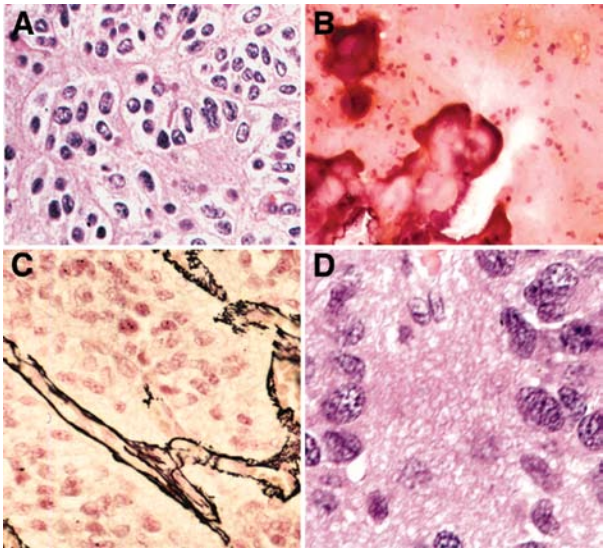

Figure 2.

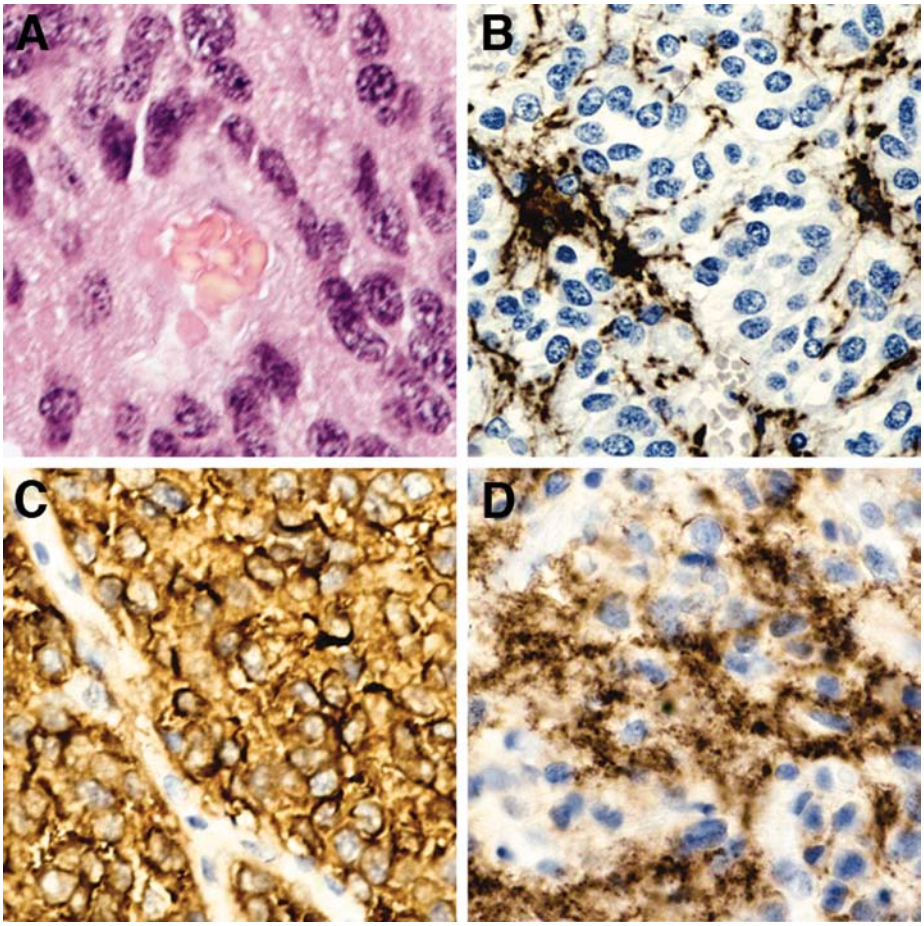

Figure 3.

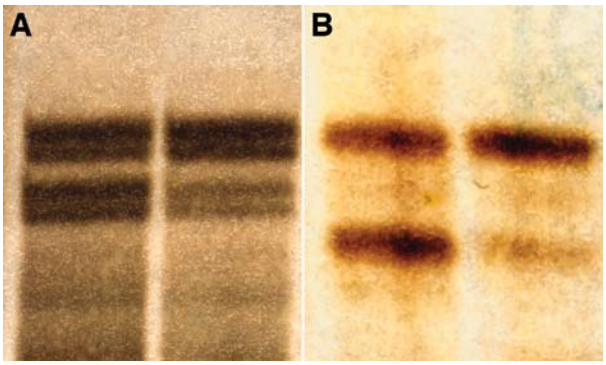

Figure 4.

MOLECULAR PATHOLOGY

PCR based loss of heterozygosity (LOH) analysis was performed. Multiple microsatellite polymorphic tetranucleotide markers on the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) were used. All amplified products lied within the common region of deletion for oligodendrogliomas. Leukocyte DNA of the patient was available for analysis of the constitutional allele status. A loci was coined "informative" in case of heterozygosity for the investigated allele. LOH 1p and 19q for all informative loci was demonstrated. Figures 4A and 4B show representative examples of informative loci on 1p and 19q, respectively. Corresponding leukocyte DNA is paired with tumor DNA. In the tumor DNA one of the 2 alleles, constitutively present in the leukocyte DNA, is lost.

DIAGNOSIS

Oligodendroglioma WHO grade II with neurocytic differentiation.

DISCUSSION

Recently 4 cases of this new and distinctive glioneuronal tumor composed primarily of oligodendroglioma and, to a lesser extent, neurocytoma-like regions with rosette formation have been described (4). Based on clinicopathologic and genetic features the authors devised the term "oligodendroglioma with neurocytic differentiation". There are striking clinical, morphological and genetic similarities between these and the present case. All were frontal lobe tumors. Three of the 4 arose in the left hemisphere. The mean age of onset was 43 years. The tumors carried overlapping morphological and immunohistochemical features of oligodendrogliomas and central neurocytomas. In one of the 4 microcalcifications were noted. Despite extensive morphological overlap, there are distinct clinicopathologic and genetic alterations in oligodendrogliomas and central neurocytomas. In contrast to oligodendrogliomas often arising in the frontal lobe, central neurocytomas are rare neoplasms principally found adjacent to the foramen of Monro (2, 8). Extraventricular tumors with neurocytoma- like morphology should therefore include the differential diagnosis of an oligodendroglioma with neurocytic differentiation.

Genetically, the incidence of combined LOH 1p and 19q, the "molecular signature" for the majority of oligodendroglial neoplasms (3), is very low in central neurocytomas (7). Furthermore, central neurocytomas with LOH 1p and LOH 19q show randomly distributed allele losses affecting single chromosomal loci only (7). Molecular pathology proves to be a feasible diagnostic tool in these cases. Indeed, as in our case, combined LOH 1p and LOH 19q was demonstrated in three of the four reported tumors for all informative loci (4). Incidentally, all these tumors—like the presented one here—were located in the left frontal lobe.

The histogenesis of oligodendroglioma is still not understood. So far the O-2A cell, identified in rodent models with the ability to differentiate along either oligodendroglial or astrocytic lines depending on cell culture conditions is considered a potential progenitor cell (5). Recently, Williams et al. have isolated a precursor cell from the rat cerebral cortex capable of generating both neurons and oligodendrocytes proposing the existence of a "N-O" precursor cell (9). While oligoastrocytomas might be explained by the existence of an O-2A precursor cell, oligodendrogliomas with neurocytic differentiation might originate from the "N-O"- cell. It is unknown, however, if "O-2A"-cells or "N-O" -cells exist in humans at all. While these tumors might answer questions as to the origin of oligodendroglial neoplasms in the future, it is important for today's neuropathologist to be aware of this variant of oligodendrogliomas. Their clinical course, despite a tendency of recurrence, seems benign. Moreover, alternative therapeutic strategies arise, if LOH 1p and LOH 19q is demonstrated, as in this case. Oligodendrogliomas with allelic losses on these chromosomes proofed to be chemosensitive tumors and patients with these tumors were longer recurrence free and had an longer overall survival time (1, 6).

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