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Research Article

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Giant cell glioblastoma in childhood-Pathohistological and immunohistochemical analysis, forecast and complex treatment

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Abstract

A six year old child is presented with giant cell glioblastoma multiforme. The importance of pathohistological and immunohistochemical analysis is discussed for the diagnosis of this rare pathohistological subtype glioblastoma in childhood. The Magnetic Resonance Image Characteristics, unfavorable prognosis and high cancer cell resistance to radiotherapy (RT) and chemotherapy (Ch) are also highlighted. The risk of local recurrences and tumor progression is high, despite the complex treatment, including visibly total tumor surgery, postoperative RT and adjuvant Ch. By this pediatric clinical case of childhood giant cell glioblastoma multiforme, we emphasize the emerging need to optimize early diagnostics and the multidisciplinary healing approach.

Keywords: Giant cell glioblastoma multiforme, Childhood brain tumor, Surgery, Postoperative radiotherapy, adjuvant chemotherapy, Multidisciplinary treatment

Introduction

The giant cell glioblastoma (GCG) is rare aggressive brain neoplasm predominantly comprised of multinucleus giant cells with abundant eosinophilic cytoplasm [1]. For the first time this histology was published by Schmincke, and the name "giant cell glioma" was defined by Meyer in 1913 [2,3]. GCG is diagnosed in 1%-5% of all glioblastomas multiforme (GM) [4-9]. Recent studies report for an incidence of 1% in adults and 3% in children among all glioblastoma cases [10]. This aggressive brain neoplasm is a patomorphological subgroup of GM, extremely rarely diagnosed in childhood [8,11]. Despite multimodal treatment, average overall survival is only 12 months [1]. Through this clinical case we are trying to expand the scarce database associated with pathohistological tumor characteristics, imaging diagnostics and multimodal treatment of this rare children's brain tumor.

Clinical Case

We present a 6 year old child with headaches, vomiting and drowsiness. MRI of the brain performed in July 2014, revealed brain tumor in a left frontal area. The first operation was with a volume of biopsy (dotting of the tumor cystic part). in August 2014, due to symptoms related to increased intracranial pressure, a subtotal tumor surgery, one cycle Ch (Vincristin, Etoposide and Cisplatin), Intensity Modulated Radiotherapy (IMRT) by VMAT technique up to total dose (TD) 56 Gy with daily dose (DD) 1.8 Gy and followed by four cycles Ch with Etoposide, Cisplatin and Cyclophosphamide were performed. Control MRT in January 2015 visualizes local tumor relapse. In February 2015, reoperation -Adimo total tumor exhibition was carried out. Treatment continued with 6 cycles Temozolomide. Control MRT in April 2015 established tumor progression. The child is considered as inoperable. Due to brain edema with increased intracranial pressure, anti-edematous and symptomatic treatment was performed. The child died In July 2015.

From the Studies Histological Result

Glioblastoma multiforme, giant cell subtype, G4 on the World Health Organization (Figure 1). MRT of a core brain before visibly total tumor excision/August 2014-cystic annular-contrast capturing lesion in a left front-parietal area with a maximum diameter of 46 mm (Figure 2 and Figure 3).

Control CT of a brain after visibly total tumor excision/August 2014: Data on a small suprai and subdural effusion under the bone

lambo left supratventorially frontocally and front with lightweight compression and dislocation to the right of the left-handed horn of the left-handed ventricle. Diffuse edema of left largebrain hemisphere (Figure 4). Intensity modulated radiotherapy (IMRT) on VMAT technology in the tumor bad up to TD 56 Gy with DD 1.8 Gy under the protection of anti edematous drugs and anti-inflammatory therapy was conducted (Figure 5).

Control MRT/January 2015: After RT and after four cycles Ch by Etoposide, Cisplatin and Cyclophosphamide- Date for a new circle lesion parasigital to the left with a diameter of 12.5 mm, involving corpus callosum, grown to 15x10 mm. After contrasting increases the signal. Intraoperative/February 2015-Two recurrent tumor nodes with a macroscopic type of high-level glioma are visualized, which are visibly totally eliminated. One of the nodes is depth of the middle frontal girus, back from the porencephal cyst on the left and another cyst on the left, engaging the knee of the corpus callosum and reaching contralateral roof of right lateral ventricle to the head of the nucleus caudatus.

Control MRT/April 2015: Residual tumor connected to the wall of the porencephal cyst and prominent to a corpus callosum.

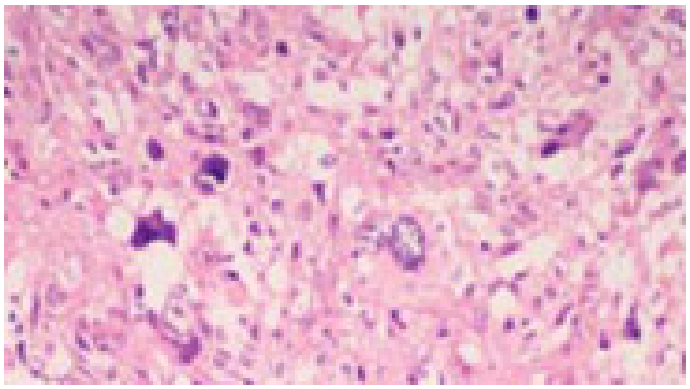

Figure1: Photomicrograph of giant cell multiforme glioblastoma showing plomorphic giant astrocytes/H&E x100.

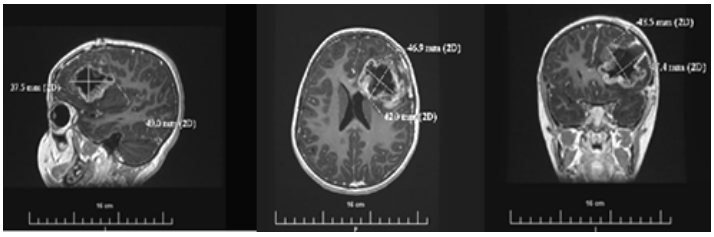

Figure 2: MRT with contrast/sagittal, axial and frontal images -Annular contrast accumulating formation in left frontoparietal area with maximum diameter of 46 mm.

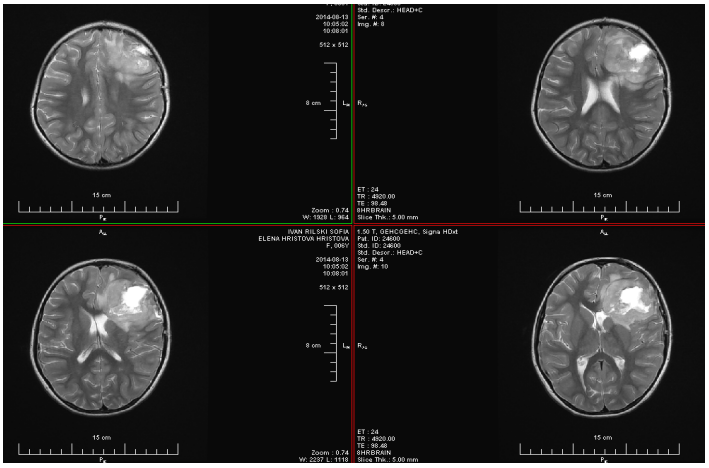

Figure3: Axial MRT-FLAIR images of a frontoparietal tumor, located on the left with non-homogeneous postcontrast accumulations with approximate edema and mass- effect.

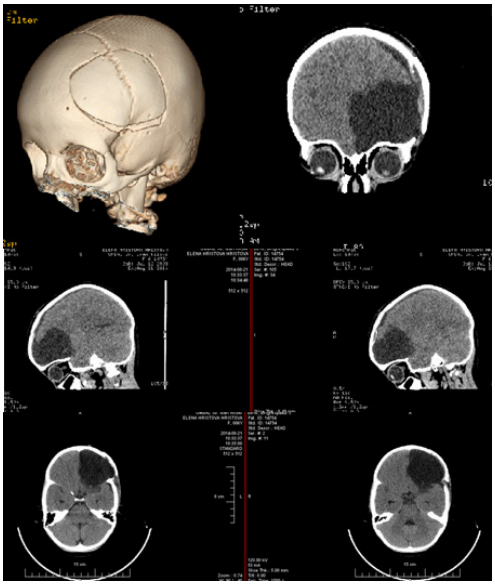

Figure 4: Postoperative CT after fronto-parietal craniotomy with visibly total tumor excision.

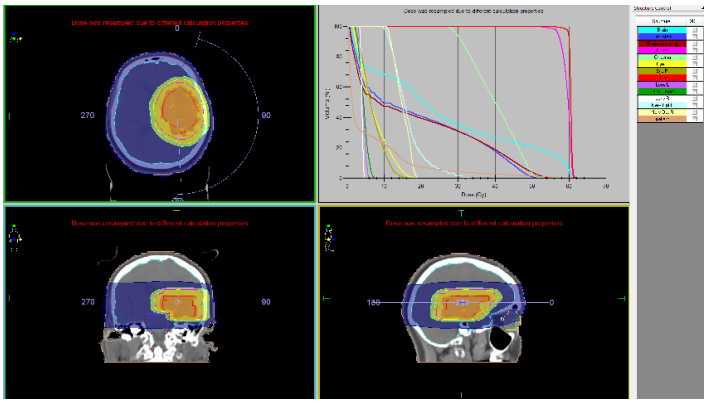

Figure 5: Intensity Modulated Radiotherapy by VMAT technique up to TD 56 Gy with DD 1.8 Gy.

Discussion

In childhood, the giant cell glioblastoma multiforme (GCG) occurs in 0.2% of all brain neoplasms [12,13]. Clinical cases in children below 10 years of age are 6% and those between 10-20 years. 9% of all brain tumors [14]. The glioblastoma multiforme IDH wild type encompasses giant cell glioblastoma, gliosarcoma and epithelioid glioblastoma [15]. The GCG is a rare subgroup of glioblastomas diagnosed in 5% of all multiforme glioblastomas [16] It is most commonly diagnosed as a supratentorial lesion, mostly in the temporal brain [17]. It is seldom diagnosed frontal, parietal or cerebellar GCG localization, as well as a multifocal tumor [18-20].

Pathohistological Characteristics and Immunohistochemistry

The presented rare clinical case emphasizes on a number of important aspects. First of all, the aggressive pathologistological variant "giant cell glioblastoma" with analaplastic ultimate undifferentiated glial cells with high mitotic activity (Figure 1). GCG is an aggressive, WHO grade IV, diffuse glioma of astrocytic lineage featuring cellular pleomorphism, nuclear atypia, mitotic activity, diffuse growth pattern, microvascular proliferation or necrosis [15]. It mainly contains pleomorphic, giant and multinucleated cells [15,21] along with a abundant reticular stroma and high frequency of P53 mutations [8,18,22]. The characteristic pathohistological morphology of GCG consists of abundant, bizarre appearing tumor giant cells, many multinucleated, smaller fusiform cells, extensive necrosis, brisk mitotic activity, abundant stromal reticulin and occasional perivascular lymphocyte cuffing [9]. Immunohistochemical analysis of tumor cells reports positive expression of the tumor cells revealed glial fibrillary acidic protein (GFAP), which suggested an astroglial origin, positive expression for S100, vimentin, p53, beta III tubulin [9,21] and negative for EMA (epithelial membrane antigen) [10]. Alpha I-antitrypsin was detected with relatively high frequency in the giant cells, and its presence may explain their bizarre sizes and pericellular reticulin fiber formation [23].

Image Diagnostics

Giant cell glioblastoma is observed typical CT and MRI image: Hipotense cystic lesion of T1 and T2, annular accumulating contrast and necrosis. These changes are associated with the approximate edema and the MASS-effect [8]. This typical MRT image is visible very clearly on Figure 2. The FLAIR image presents a left cerebral frontoparietal tumor with nonhomogeneous post-contrast accumulations, approximated edema and MASS-effect (Figure 3).

Prognosis

In principle, glioblastomas are aggressive brain neoplasms with poor prognosis and average survival 10-12 months [24-26]. Of the surveys comparing the survival of the GCG with the classic GM variant, there are better healing results in the average survival of 11 months, while in the classic subtype survival is only 8 months [4-7,21,27-34]. Reported 5 years survival for GCG is barely 0.5%-5% [35-38]. For GCG patients, factors influencing survival included age at presentation, tumor size, extent of resection, adjuvant RT use and tumor atypical locations (i.e., brainstem, ventricle, or cerebellum) [1,8]. In this neoplasm lymphocytes seem to play a major prognostic role and giant-monstrous cells are indirectly implicated, reasonably enhancing the host's immune response by magnifying the antigenic stimulus [4]. The larger volume of neurosurgical operation is associated with a better forecast [39]. In the clinical case presented, despite the two-time visible total tumor excision of the primary tumor and marginal relapse, we monitored rapid expansion of residual tumor cells. We reported significant tumor progression against the background of adjuvant RT and Ch due to the exceptional radio- and chemoresistance of giant glioblastoma cells.

Complex Treatment

Among high-malignancy gliomas, children's multiforme glioblastoma is a particular challenge in terms of therapeutic behavior [11,15,40-42]. The curative benefit of the maximum safe tumor resection followed followed by adjuvant RT [4,43-46], or by an adjuvant RT combined with Ch [47]. Patients who did not have a gross total resection have a higher mortality rate [48]. The most effective complex treatment that improves the survival of patients includes surgery combined chemo-radiotherapy as well as prolonged adjuvant chemotherapy with Temodal, which is the standard GCG treatment in childhood [49-52]. Despite the progress of neurosurgery and adjuvant antitumor treatment, average survival is only 12 months, without significant improvement over the last 30 years[53-54]. Temodal was introduced as efficient chemotherapy (Ch), but its application (simultaneously or adjuvant with RT) prolonged overall survival by 2 months [55]. Postoperative RT with radical doses over TD 54Gy significantly improves GCG survival [56,57]. Early diagnosis with gross total resection and adjuvant chemotherapy might increase the survival period [10]. The healing results are not optimized, despite the introduction of hyperfractionated RT and high-tech radical techniques such as IMRT and Cyberknife RT [50,58]. In the clinical case, we reported 12 months survival, despite the complex treatment including three operations, IMRT with a high radical dose and adjuvant Ch. This unsatisfactory survival is similar to the number of authors published in the medical literature [1,4,28].

Conclusion

The giant cell glioblastoma in childhood is extremely rare and aggressive brain neoplasm. The prognosis remains poor, despite multimodal treatment, including multiple operations, postoperative RT and adjuvant Ch on various regimens. GCGB in childhood is an extremely radio- and chemoresistance tumor. The radio- and chemoresistance, as well as the aggressive malignant characteristics of giant glioblastoma cells are associated with high risk of local recurrences. To increase cellular radiosensibility and improvement of healing results, early diagnosis is required, applying high technological radiation in larger volumes combined with chemotherapy or targeted therapy.

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