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Research Article

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Multiple Malignant Meningiomas Presenting As Thrombocytopenia

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Abstract

Backgrounds: *Malignant meningiomas are CNS tumors arising from the arachnoids cap cells of the meninges, very rare in infants. Clinically, intracranial hypertension or focal neurological deficits are usually seen for mass effect, rather than leukemoid symptoms.*

Methods: *Retrospectively analyze the detailed clinical development, diagnosis and treatment of a 10-month-old boy initially hospitalized due to leukemoid symptoms. After careful examination, malignant meningioma (WHO grade III) was proved by the biopsy and histopathology. Chemotherapy (three cycle of ifosfamide 100 mg/kg for 3 days, plus doxorubicin 1 mg/kg for 2 days every 21 days) in combination with imatinib.*

Results: *Dura nodules significantly reduced in size, skin bleeding spots, thrombocytopenia and enlarged superficial lymph almost disappeared.*

Conclusion: *This study was conducted to demonstrate dynamic changes after effective individualized treatment. Meanwhile, we proposed that the invasiveness of meningioma induces somatic DNA damage, leading to abnormal platelet production and megakaryocytic morphology.*

Keyword: Infant, Malignant Meningiomas, Leukemoid Manifestations, Neuroimaging, Chemical Therapy

Introduction

In previous studies, Malignantmeningiomas are CNS tumors very rare in infants, and clinical symptoms are usually seen for mass effect. Meanwhile, the treatment in infants is reported rarely. In this paper; we retrospectively analyze the detailed clinical development, diagnosis and treatment of a 10-month-old boy initially hospitalized due to leukemoid symptoms. Malignant meningioma (WHO grade III) was proved by the biopsy and histopathology in the end. Novel chemotherapy (three cycle of ifosfamide 100 mg/kg for 3 days, plus doxorubicin 1 mg/kg for 2 days every 21 days) in combination with imatinib conducted good result. Finally, we analyzed the possible mechanism of his clinical manifestations.

Materials and Methods

A 10 month-old boy was initially hospitalized due to hemorrhagic spot and thrombocytopenia for 2weeks, where blood transfusion was required to maintain the platelet count. Unclassified cells were found in the bone marrow, which were similar to megakaryocytic; myeloid progenitor cells were found in peripheral blood, immunophenotype of which expressed CD41(Figure1A-C); bone marrow biopsy demonstrated extensive myelofibrosis. Above evidence suggested possible diagnosis of acute megakaryoblastic leukemia. He underwent brain MRI scan as intracranial hypertension appeared. Then the biopsy and histopathology of left frontal subdural lesion was achieved.

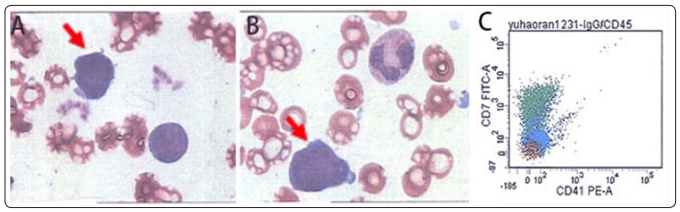

Figure 1(A, B): unclassified cells with irregular edges and cloud-like protrusions were uniform in size relatively, with a diameter of about 25 μl and little cytoplasm, which were basophilic moderately with large nucleus, rough nuclear chromatin and indistinct nucleoli. (C) Peripheral blood leukemic immunophenotype: myeloid progenitor cells express CD41

Result

Imaging findings: MR imaging revealed multiple avidly enhanced masses alongdura (Figures 2A, 2B) adjacent to flax cerebri and tentorium cerebelli, which showed iso-T1 signal intensity (Figure 2C) and mild hypo-T2 signal intensity (Figure 2D), without significant reduced diffusion (Figure 2E). Beside to lesions, thickening and enhancement of the Dura could be seen in contrast-enhanced T1 weighted image (Figure 2F), which was so called 'Dural tail sign'.

The coronal image showed internal carotid artery branch surrounded by lesions and compressive inferior sagittal sinus. Axial diffusion-weighted image showed no significantly restricted diffusion with the lesion. A marked focal masses effect could be seen in the involved brain region without secondary edema.

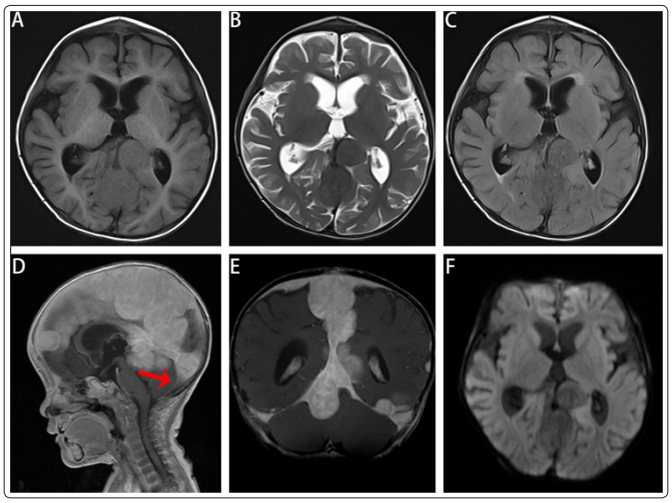

Figure 2: Multiple nodules along Dura with obvious enhancement, on Axial T1 weighted image (A) Showed iso-intensity to gray matter, on T2-weighted (B) showed hypo- intensity. Axial (C) fluid attenuation inversion recovery (FLAIR) T1 weighted MR image showed mild hypo intense lesion with respect to gray matter. Sagittal (D) and coronal (E) T1 post gadolinium enhanced images showed multiple avidly enhancing lesions with abnormal surrounding Dural thickening (red arrow). Coronal image shows internal carotid artery branch surrounded by lesions (red angle) and compressive inferior sagittalsinus (red thin arrow). Axial (F) diffusion-weighted MR image shows no significantly reduced diffusion with the lesion.

Histopathology examination (Figure 3A-C): The tumor was composed of fuse form cells densely arranged in bundles or sheets with nuclear pleomorphism and granular nuclear chromatin, where nucleolus could be seen in individual cells. The mitoses occurred over a rate of 20/10 HPF, where many apoptotic bodies and karyorrhexiscould be seen. Immunohistochemically, the tumor cells were positive for Ki-67 protein, leading to a final diagnosis of met plastic (malignant) meningioma (WHO grade III).

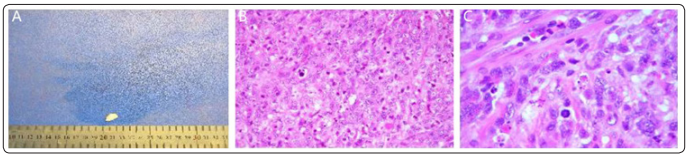

Figure 3: Left frontal subdural lesion. (A) A piece of yellow soft tissue with size of 1.5 cm * 0.8 cm * 0.7 cm. (B) fusiform cells densely arranged in bundles or sheets (hematoxylin-eosin, original Magnification×20 objective). (C) Cells with Nuclear pleomorphism and granular nuclear chromatin, Where nucleolus could be seen in individual cells. The mitoses occurred over a rate of 20/10 HPF, where many apoptotic bodies and karyorrhexis could be seen (hematoxylin-eosin, original magnification×40objective).

Immunohistochemistry: Vimentin (+), INI-1 (SNF5) (+), Ki-67 (about 60% +), EMA (-/ +) According to the EpSSG NRSSTS 2005 protocol, chemotherapy (three cycle ofifosfamide100 mg/kg for 3 days, plus doxorubicin 1 mg/kg for 2 days every 21 days)in combination with imatinib. As a result, Dura nodules significantly reduced in size, skin bleeding spots, thrombocytopenia and enlarged superficial lymph almost disappeared. The brain MRI scan (Figure 4.1A-D) 2 days after chemotherapy showed masses size reduce compared with previous exam. In addition, the brain MRI scan 2 months after chemotherapy (Figure 4.2A-D) showed significantly hypo-T2 signal intensity, which may be related to the apoptosis of tumor cells. The brain MRI scan 3 months after chemotherapy (Figure 4.3A-D) indicated slightly increased size of lesions.

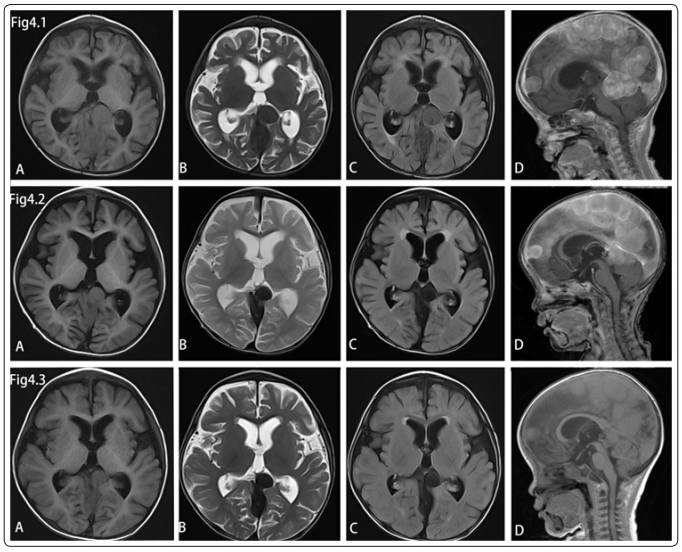

Figure 4.1 superior A-D: Axial T1 (A) showed that the lesions were little bit smaller than before. T2 weighted (B) and Axial (C) fluid attenuation inversion recovery (FLAIR) T1 weighted MR image show that signal intensity of lesion was little bit lower than before. Sagittal (D) T1 post gadolinium enhanced image shows reduced range of lesion than before.

Figure4.2 intermediate A-D: Axial T1 (A) shows that the lesion is significantly smaller than before.T2 weighted (B) and Axial (C) fluid attenuation inversion recovery (FLAIR) T1 weighted MR image show that signal intensity of lesion is significantly lower than before. Sagittal (D) T1 post gadolinium enhanced image shows reduced range of lesion than before.

Figure 4.3 inferior A-D: Axial T1 (A) shows that the lesion is slightly bigger than before. T2weighted (B) and Axial (C) fluid attenuation inversion recovery (FLAIR) T1 weighted MR image show similar signal intensity of lesion to before. Sagittal (D) T1 post gadolinium enhanced image shows increased range of lesion than before.

Discussion: Acute megakaryocytic leukemia is a rare subtype of acute myeloid leukemia (AML) caused by primitive megakaryoblasts arrested at a certain stage of differentiation and proliferated abnormally [1]. Clinical symptoms were similar in many respects to those observed in patients with other types of acute leukemia and included progressive pallor, bleeding, bone pain and palpable liver. And most patients have high WBC and low PLT [2]. The diagnostic criteria of children acute megakaryocytic leukemia are; visible megakaryocytic in peripheral blood; bone marrow nucleated cells in the original + naive megakaryocytic ≥ 30%; bone marrow dry pumping, with bone marrow fibrosis; bone marrow biopsy seen

increased primary megakaryocytic, net The increase of febrile fibers; electron microscopy confirmed platelet peroxide (PPO) positive; immunophenotype confirmed leukemic cell immune phenotype was CD61, CD42 or CD41 positive [3, 4].

This patient was mainly characterized by hemorrhagic spot and thrombocytopenia, where blood transfusion was required to maintain the platelet count (Table 1). Besides, bone marrow cytology revealed that unclassified cells morphology was similar to megakaryocytic, peripheral blood immunophenotype expressed CD41. Above support the diagnosis of acute megakaryocytic leukemia. For all that, the percentage of unclassified cells was less than 30%, which did not reach the diagnostic criteria of acute megakaryocytic leukemia.

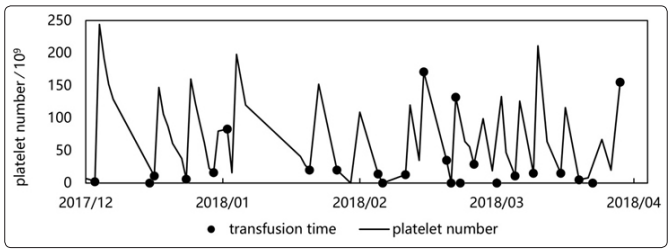

Table 1: Changes in platelet number during 2017.12.28-2018.4.24

Meningioma is one of the CNS tumors originating from the arachnoids cap cells of the meninges, which is classified into three grades according to the WHO classification: grade I (benign), grade II (atypical), grade III (met plastic/malignant) [5]. Meningiomas of children and adolescents are rare, accounting for 0.4%-4.6% of CNS tumors in the population, of which 7%-38% tend to be malignant, 1%-2% are multiple, the ratio of male to female is 2-3:1, the average onset age in children is 2-3 years old [6-11]. Radiation therapy, neurofibromatosis, and genetic factors such as familial meningiomaare the most common etiological factors [12]. Related clinical symptoms and signs depend on the location of the tumor, where the most common symptoms include increased intracranial pressure (headache, drowsiness, vomiting), focal neurological deficits in the limbs, and cranial nerve palsy. Meningioma can be located in the supratentorial and ventricles commonly, of which the most common location is the convexity of the hemispheres, while location of pediatric meningiomas often unusual. They usually present as solitary round tumors contact to the dural mater, with avidly enhancement after contrast injection. The typical features include iso-T1 signal intensity, iso or hyper intense on fluid-attenuated inversion recovery, and with obvious and homogenous enhancement following contrast injection, also with the Dural tail sign [13, 14]. The radiologic features of pediatric malignantmeningioma include an enormous size, irregular circumscription, hemorrhage, necrosis andheterogenous enhancement [15].

The histopathology features of malignant meningioma include; hypercellularity, nuclear pleomorphism, prominent nucleoli, a high mitotic index, a high nucleus/cytoplasm ratio, loss of architecture, focal necrosis and brain infiltration or metastasis [10].

With typical imaging features, the histopathology analysis of lesion is consistent with met plastic (malignant) meningioma (WHO grade III). For all that, this patient has a young age of onset without related etiological factors, whose lesions are multiple with a high degree of malignancy, as well as without focal neurological deficits, that is quite rare. However, the hemorrhagic spots, thrombocytopenia, unclassified cells of bone marrow cytology and expressed CD41 of peripheral blood immunophenotype could not be explained by meningiomas, so it is reasonable to believe that this patient also has hematologic diseases.

Michael et al. investigated 1228 patients with meningioma, 50 patients had a history of an extra cranial malignant tumors. Acute leukemia and papillary thyroid carcinoma were notable. Most of meningioma patients with a history of leukemia received radiotherapy and meningiomas were more malignant [16]. Although the blood system changes of this patient cannot be defined as a certain type of leukemia, there are two points need to be cleared. First, both malignant meningioma and some kind of leukemia occur in this patient, which is the first such case without radiation exposure reported in detail so far. Second, the patient's blood system changes are secondary tomeningioma, which can be explained an unknown antigen activated by intracranial tumor attacks platelet of the patient. It is well established that platelet is thought to form from proplatelet produced by procedural apoptosis and shedding of mature megakaryocytic [17]. However, Emma et al [18]. Found that megakaryocytic are dependent on Bcl-xL to maintain survival when they reach the point of proplatelet formation and shedding to produce platelet. DNA damage can directly inhibit the normal shedding of proplatelet. Therefore, the abnormal megakaryocytic and platelet in this patient indicates abnormal platelet production pathway. Besides, recent studies have found somatic mutations in meningiomas without NF2 mutations [19]. Therefore, we speculate that meningiomas induce somatic DNA damage, which lead to abnormal platelet formation and megakaryocytic morphology.

The mainstay of treatment for malignant meningioma is surgical resection, supplemented with radiation therapy if necessary. However, in this patient numerous nodules along Dura is reverse indications for surgical resection, is also too young to get radiotherapy, especially the difficulty in complete resection and the possibility of severe intra operative hemorrhage. The prognosis of radiotherapy is poor in such young age; especially infants at the growth and development stage are more susceptible to side effect of radiation [20]. Retrospective studies and small prospective studies evaluated arrange of drugs and demonstrated chemotherapeutic agents such as hydroxyl urea and cyclophosphamide can effectively improve progression-free survival and median overall survival in WHO grade II and III meningiomas [21].

Both ifosfamide (alkylating agent) and doxorubicin (anthracyclines antibiotic) arenon-specific cytotoxic drugs, which can prevent the proliferation of tumor cells by interfering with DNA replication [22, 23]. They can also hinder the division and proliferation of hematopoietic cells, which causes bone marrow suppression and leads to thrombocytopenia. Maurizio et al. combined the above two drugs to treat a 2-yearoldpatient with malignant meningioma and achieved good results [24]. Imatinib is a class of targeted drugs that can specifically act on platelet derived factor receptor (PDGFR) in the meningioma cell pathway to prevent tumor growth, and has been recognized to have good effects in chronic myeloid leukemia [21, 25]. According to the EpSSG NRSSTS2005 protocol for the treatment of soft tissue sarcoma, considering that the patient has thrombocytopenia, the above three drugs were combined to develop individualized treatment plan. Now the patient has completed two courses chemotherapy, the general situation has been significantly improved and the lesions have been significantly reduced. After

the third course of treatment, low-dose oral tiotipazole (an alkylatingagent that interferes with the DNA synthesis of tumor cells) and imatinib maintenance therapy were planned and followed up every 3 months to observe tumor growth and verify the efficacy of chemotherapy drugs.

References

1. Hahn AW, Li B, Prouet P, Giri S, Pathak R, et al. (2016) Acute megakaryocytic leukemia: What have we learned? Blood Rev 30: 49-53.
2. Paredes-Aguilera R, Romero-Guzman L, Lopez-Santiago N, Trejo RA (2003) Biology, clinical, and hematologic features of acute megakaryoblastic leukemia in children. Am J Hematol 73: 71-80.
3. JM Bennett DC, Daniel M (1985) Criteria for the diagnosis of acute leukemia of megakaryocytic lineage (M7): a report of the French-American-British Cooperative Group. Annals of internal 103: 460-462.
4. CK Lopez SM, M Gaudry OAB (2017) Pediatric Acute Megakaryoblastic Leukemia: Multitasking Fusion Proteins and Oncogenic Cooperations. Trends Cancer 3: 631-642.
5. Traunecker H, Mallucci C, Grundy R, Pizer B, Saran F (2008) Children's Cancer and Leukaemia Group (CCLG): guidelines for the management of intracranial meningioma in children and young people. Br J Neurosurg 22: 13-25.
6. Kotecha RS, Junckerstorff RC, Lee S, Cole CH, Gottardo NG (2011) Pediatric meningioma: current approaches and future direction. J Neurooncol 104: 1-10.
7. Sheikh BY, Siqueira E, Dayel F (1996) Meningioma in children: a report of nine cases and a review of the literature. Surg Neurol 45: 328-335.
8. Jaiswal S, Vij M, Mehrotra A, Jaiswal AK, Srivastava AK, Behari S. A clinicopathological and neuroradiological study of paediatric meningioma from a single centre. J Clin Neurosci 18: 1084-1089.
9. Maranhão-Filho P, Campos JC, Lima MA (2008) Intracranial meningiomas in children: ten-year experience. Pediatr Neurol 39: 415-417.
10. Liu Y, Li F, Zhu S, Liu M, Wu C (2008) Clinical features and treatment of meningiomas in children: report of 12 cases and literature review. Pediatr Neurosurg 44: 112-117.
11. Sakaki S, Nakagawa K, Kimura H, Ohue S (1987) Intracranial meningiomas in infancy. Surg Neurol 28: 51-57.
12. Im SH, Wang KC, Kim SK, Oh CW, Kim DG, et al. (2001) Childhood meningioma: unusual location, atypical radiological findings, and favorable treatment outcome. Childs Nerv Syst 17: 656-662.
13. Tufan K, Dogulu F, Kurt G, Emmez H, Ceviker N, et al. (2005) Intracranial meningiomas of childhood and adolescence. Pediatr Neurosurg 41: 1-7.
14. Takeguchi T, Miki H, Shimizu T, Kikuchi K, Mochizuki T, et al. (2004) The dural tail of intracranial meningiomas on fluid-attenuated inversion-recovery images. Neuroradiology 46: 130-135.
15. Zhang H, Rödiger LA, Shen T, Miao J, Oudkerk M (2008) Preoperative sub typing of meningiomas by perfusion MR imaging. Neuroradiology 50: 835-840.
16. Sughrue ME, Kane AJ, Shangari G, Parsa AT, Berger MS, et al. (2010) Prevalence of previous extra cranial malignancies in a series of 1228 patients presenting with meningioma. J Neurosurg 113: 1115-1121.
17. Galluzzi L, Joza N, Tasdemir E, Maiuri MC, Hengartner M, et al. (2008) No death without life: vital functions of apoptotic effectors. Cell Death Differ 15: 1113-1123.
18. Josefsson EC, James C, Henley KJ, Debrincat MA, Rogers KL, et al. Megakaryocytes possess a functional intrinsic apoptosis pathway that must be restrained to survive and produce platelets. J Exp Med 208: 2017-2031.
19. Clark VE, Erson-Omay EZ, Serin A, Yin J, Cotney J, et al. (2013) Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science 339: 1077-1080.
20. Vinchon M, Leblond P, Caron S, Delestret I, Baroncini M, et al. (2011) Radiation-induced tumors in children irradiated for brain tumor: a longitudinal study. Childs Nerv Syst 27: 445-453.
21. Kaley T, Barani I, Chamberlain M, McDermott M, Panageas K, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. Neuro Oncol 16: 829-840.
22. Liptak JM, Forrest LJ (2007) with row & MacEwen's Small Animal Clinical Oncology. Surgical approach to oral tumors use of CT 4th edition. St. Louis (MO): Saunders/Elsevier 2007: 163-192.
23. Momparler RL, Karon M, Siegel SE, Avila F (1976) Effect of adriamycin on DNA, RNA, and protein synthesis in cell-free systems and intact cells. Cancer Res 36: 2891-2895.
24. Lucchesi M, Buccoliero AM, Scoccianti S, Guidi M, Farina S, et al. (2016) A successful case of an anaplastic meningioma treated with chemotherapy for soft tissue sarcomas. CNS Oncol 5: 131-136.
25. Gambacorti-Passerini C, Antolini L, Mahon FX, Guilhot F, Deininger M, et al. (2011) Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. J Natl Cancer Inst 103: 553-561.