Atypical teratoid/rhabdoid tumor. A posterior fossa tumor, case report and review of literature

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ABSTRACT

Atypical teratoid/rhabdoid tumor (AT/RTs) is a highly malignant nervous system tumor, occurs primarily in very young children. These tumors are distinctive, malignant neoplasms of uncertain histogenesis. They are thought to be embryonal and are usually composed of varying amounts of rhabdoid cells, small primitive neuroepithelial cells, epithelial tissue and neoplastic mesenchymal components. This is a case of AT/RT in a four years male patient who presented to the department of neurosurgery at Ibn-Sena Teaching Hospital, complaining of headache, nausea and vomiting for the last two months, progressed to visual disturbance and limbs weakness. Computerized tomography showed an ill-defined large mixed density posterior fossa tumor associated with hydrocephalus. Urgent ventriculoperitonial shunt followed by craniectomy and excision of the cerebellar tumor were performed. Histologically, according to the complex heterogeneity of cell types and tissue components, tumor was diagnosed as AT/RT and confirmed by immunohistochemical study.

Keywords: Atypical teratoid/rhabdoid tumor, posterior fossa tumor.

الورم اللانمطي العَصَوِيّ / المسخي. ورم الحفّرة الخلفّية، حالة مسجلة ومراجعة للمقالات

الخلاصة

الورم اللانمطي العَصَوِيّ / المسخي هو ورم سرطاني شديد يصيب الجهاز العصبي، ويصيب مبدئيا الأطفال الصغار. وهي أورام سرطانية غير مؤكدة منشأ التكوين النسيجي. أعتقد بانها مُضْغِيّ، ومتكون من كميات متفاوتة من الخلايا العَصَوِيّة، خَلاَيا عَصَبِيَّةٌ ظِهارِيَّة بِدائِيّ، نسيج ظِهارِيَّ و مكونات ورمية اللُّحْمَةِ المُتَوَسِّطَة. هذه حالة مسجلة من ورم اللانمطي العَصَوِيّ/ المسخي لطفل ذكر يبلغ من العمر ٤ سنوات والذي قدم الى قسم الجملة العصبية في مشفى ابن سينا التعليمي يشتكي من الآم الرأس مع غثيان و تقيء وللشهرين الأخيرين. وبعدها تطورت الحالة إلى إضطراب النظر وضعف الأطراف الأربعة. التصوير الطبقي الشعاعي كشف عن وجود ورم غير محدد، متفاوت الكثافة في الحفرة الخلفية للدماغ مع تكون مَوَهُ الرَّأْس. أجريت له عملية مستعجلة لتحويل بطيني صفافي، ومن ثم عملية إستئصال للورم. عِيانِيّا: الورم كان كبيرا ومُصْمَت، مع مناطق تنخر. مجهريا وبالإعتماد على التركيب النسيجي المعقد للورم من مزيج الخلايا والأنسجة المختلفة تم تشخيص الورم باللانمطي العَصَوِيّ / ألمسخي والتي تم إثباتها بالصبغات الكِيمْيائِيَّة الهيستولوجيَّة المَناعِيّة.

ألكلمات المميزة: ورم اللانمطي العَصَوِيّ/ المسخي، ورم الحفرة الخلفية.

Atypical teratoid/rhabdoid tumor (AT/RT) is a highly malignant, increasingly recognized central nervous system tumor that primarily occurs in very young children, most often in children younger than two years of age, although there were reports of cases in older children and adults[1,2,3].

This tumor was first described in 1987, but was not defined as a distinct entity until 1996 by Rorke et al[4,5]. This tumor was often classified as medulloblastoma, primitive neuroectodermal tumor, or choroid plexus carcinoma. This is understandable since approximately two-thirds of AT/RT have components that resemble

medulloblastoma or primitive neuroectodermal tumor[6]. Because histologically AT/RT resembles the rhabdoid tumor of the kidney, it had sometimes been referred to as malignant rhabdoid tumor of the brain or central nervous system before it was recognized as a distinct tumor type[7]. Atypical teratoid/rhabdoid tumor was included for the first time in the World Health Organization classification of tumors of the CNS in 2000[8].

Atypical teratoid/rhabdoid tumor shows characteristic immunohistochemical features, which tend to aid in its differentiation from primitive neuroectodermal tumor. Ninety five percent of these tumors are positive for epithelial membrane antigen and vimentin, and 75% for smooth muscle actin. The primitive neuroectodermal cells variably express neurofilament protein (NFP), glial fibrillary acidic protein (GFAP), keratin or desmin. AT/RT are rapidly growing tumors that can have MIB-1 labeling indices of 50%–100%[8,9,10]. In addition the loss of nuclear expression of INI1 (hSNF5/BAF47) is diagnostic of AT/RT of the central nervous system[11].

CASE REPORT

This four years old child presented with history of headache for two months, more intense in morning associated with nausea and vomiting. Initially the headache was irregular and intermittent, but in the last month occurred daily. The patient then started to get disturbance of vision, abnormal eye gaze and weakness of the four limbs. Ophthalmoscopic examination showed bilateral gross papilledema. MRI scan revealed a large ill-defined hypo- and hyper mixed intensity mass in the posterior fossa involving brain stem and extending to the cerebellar hemisphere and cerebellopontine angle (CPA) with evidence of hydrocephalus involving lateral and third ventricles (**Fig. 1**). Radiologically, two diagnoses were proposed; high grade glioma and medulloblastoma.

Urgent ventriculoperitonial shunt was performed. Tumor was fixed in the brain stem and extending to the cerebellar hemisphere and cerebellopontine angle (CPA). Sub-occipital craniectomy and total tumor excision were performed. Postoperatively the patient had good neurological recovery and his CT-scan showed no visible residual tumor (**Fig. 2**).

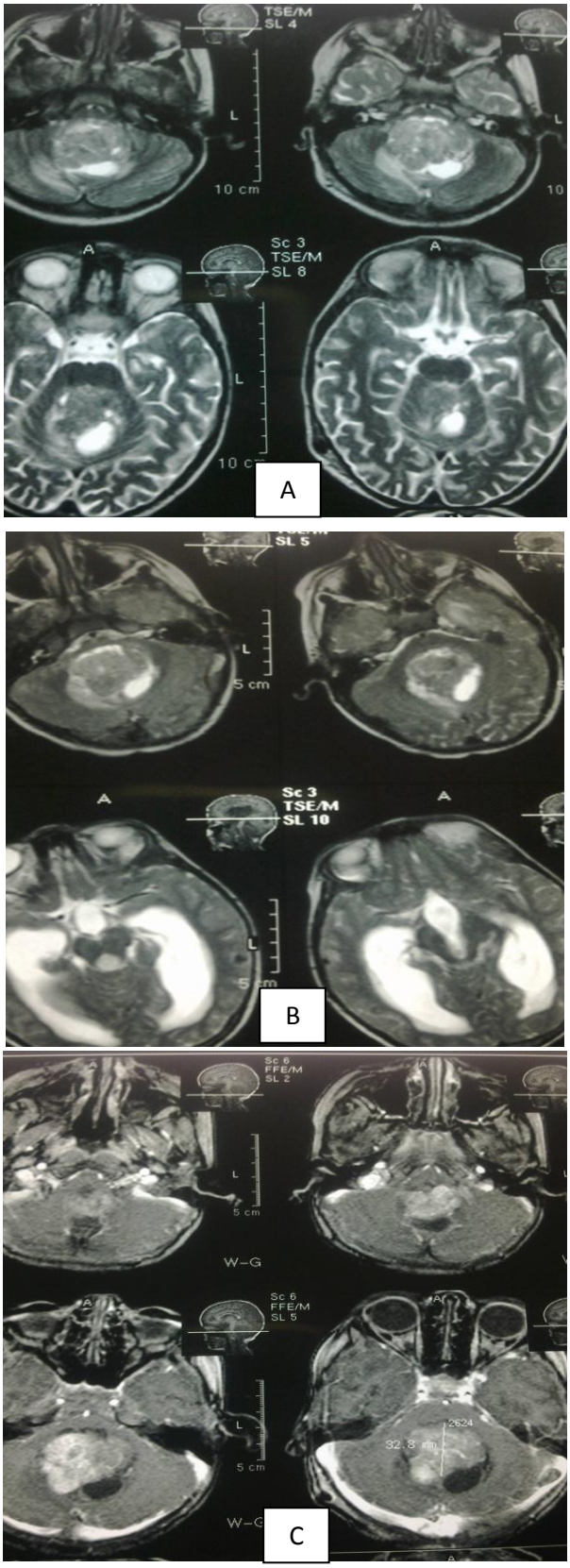


Figure 1. Preoperative MRI scan
A; Infiltrative posterior fossa tumor.
B; Hydrocephalus of the lateral and third ventricles.
C; Hypo and hyper- intense areas.

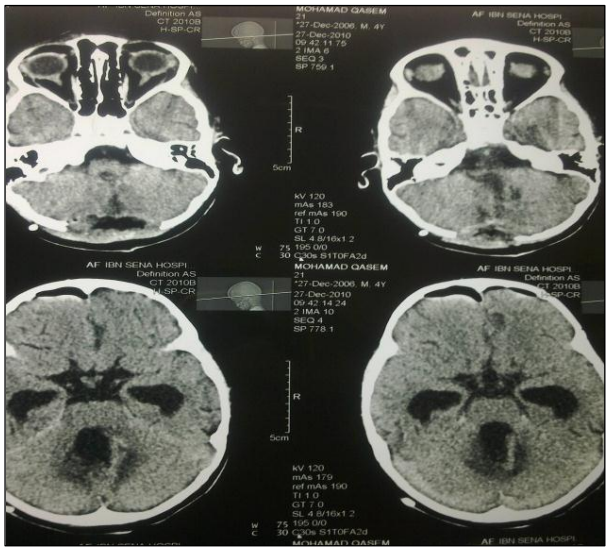
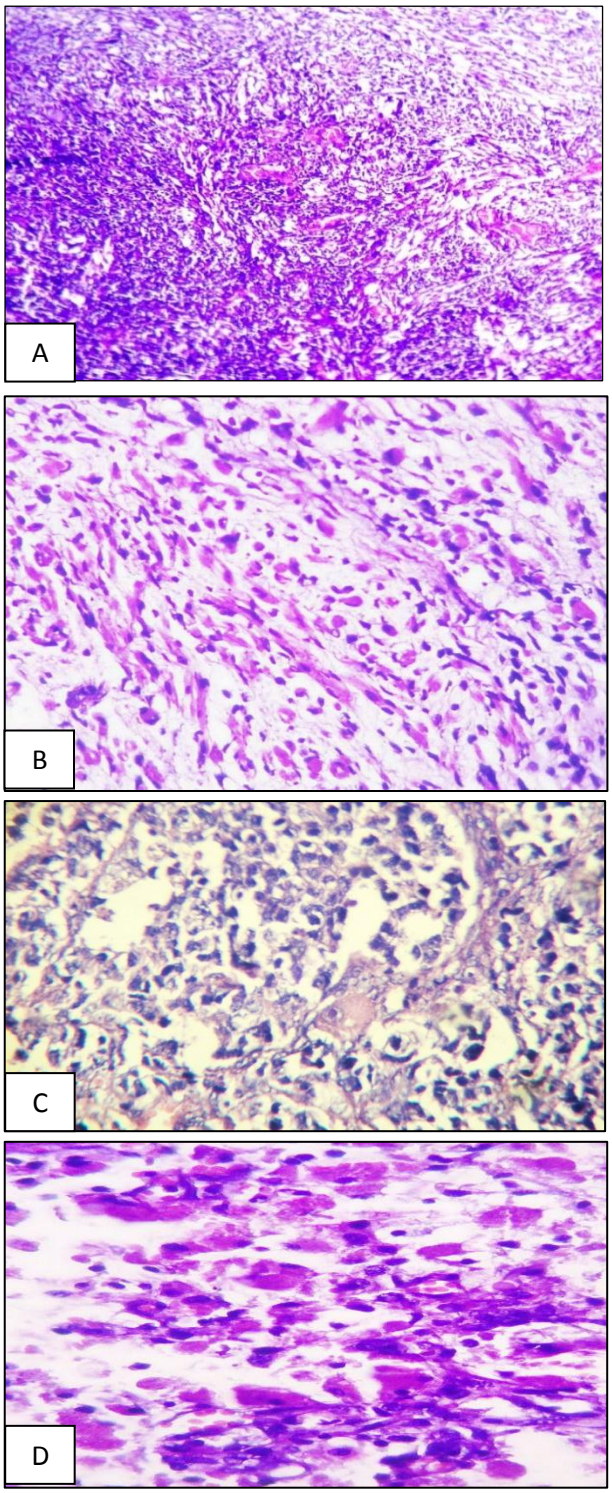


Figure 2. Postoperative CT-scan: No residual tumor.

Macroscopically, tumor was irregular solid whitish-gray, measuring 5.5 x 4.0 x 3.0 cm. microscopically it was composed of hybrid of typical rhabdoid cells, primitive neuroectodermal medulloblastoma/PNET-like cells, multinucleated giant cells, and cells with fine granular eosinophilic and water-clear cytoplasm. Background stroma consisted of collagenous and myxoid tissue with skeletal muscle differentiation enriched by thick wall blood vessels. Areas of necrosis were also present (**Fig. 3**).

Immunohistochemical profile; rhabdoid cells and epithelial elements were strongly positive for EMA, cytokeratin and vimentin, whereas the other neuroepithelial and mesenchymal components were focally positive for GFAP, SMA and desmin (**Fig. 4**).



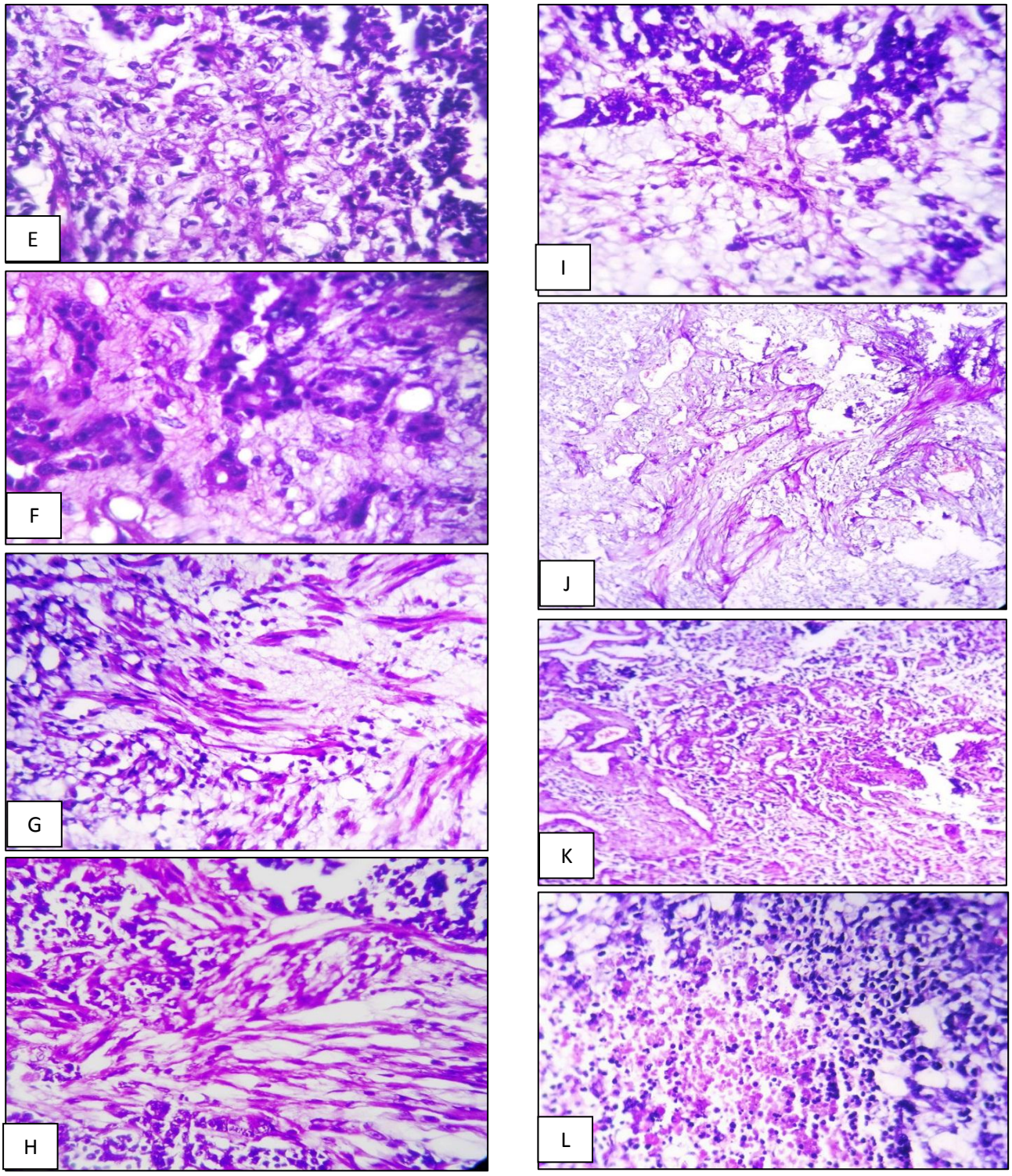


Figure 3. A; Medulloblastoma/PNET-like areas (H&E; x100). B; Rhabdoid cells (H&E; x400). C; Rhabdoid cells with vesicular nuclei, prominent nucleolus and intracytoplasmic eosinophilic inclusion (H&E; x400). D; Cells with fine granular eosinophilic cytoplasm (H&E; x400). E; Cells with water-clear cytoplasm (H&E; x400). F; Epithelial and ependymal tubes (H&E: x400). G; Skeletal muscle differentiation (H&E; x400). H; spindly mesenchymal component (H&E: x400). I & J; Myxoid (H&E; x400) and collagenous stroma (H&E; x200). K; high vascularity (H&E: x200). L; focus of necrosis (H&E: x400).

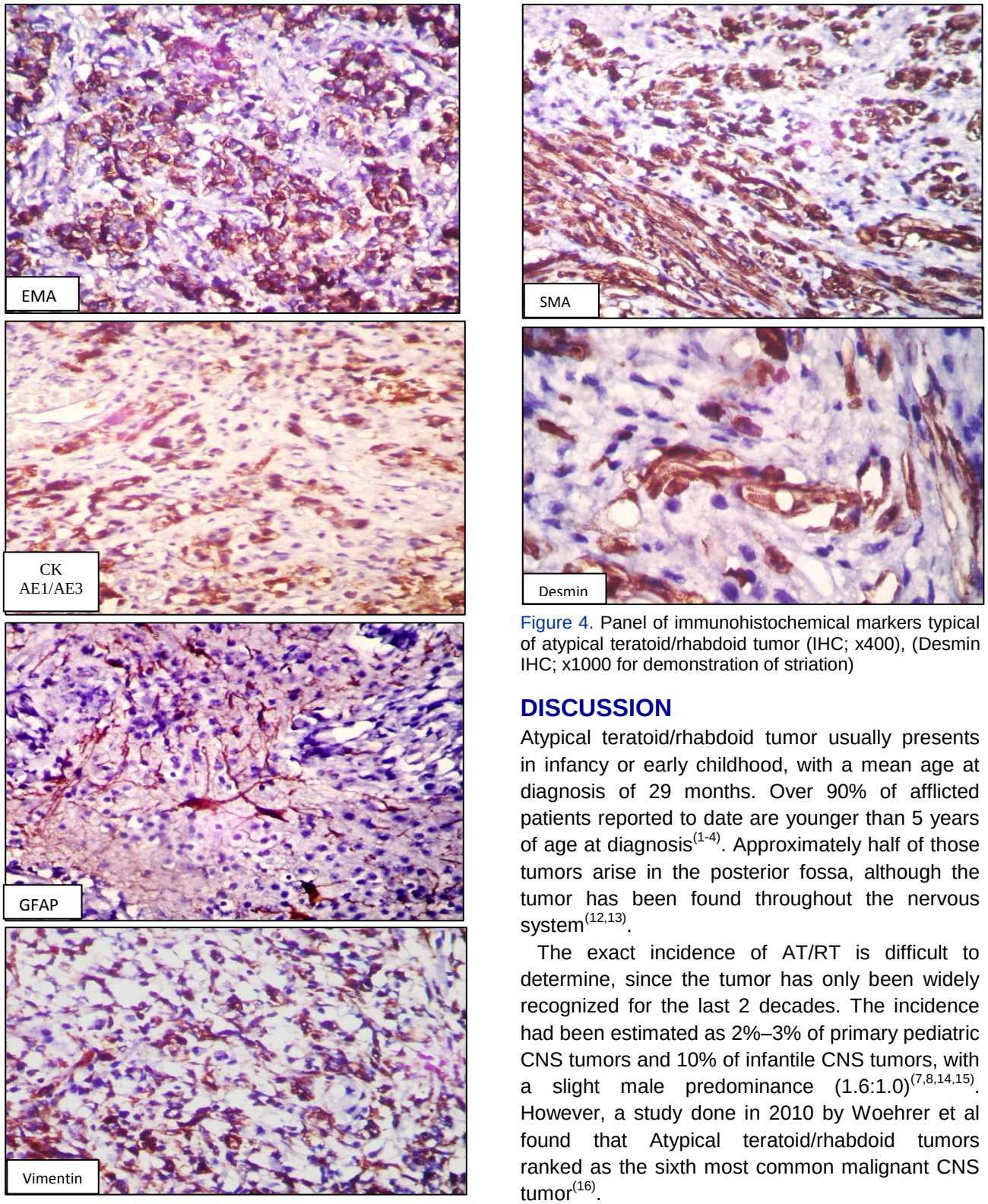


Figure 4. Panel of immunohistochemical markers typical of atypical teratoid/rhabdoid tumor (IHC; x400), (Desmin IHC; x1000 for demonstration of striation)

DISCUSSION

Atypical teratoid/rhabdoid tumor usually presents in infancy or early childhood, with a mean age at diagnosis of 29 months. Over 90% of afflicted patients reported to date are younger than 5 years of age at diagnosis[1-4]. Approximately half of those tumors arise in the posterior fossa, although the tumor has been found throughout the nervous system[12,13].

The exact incidence of AT/RT is difficult to determine, since the tumor has only been widely recognized for the last 2 decades. The incidence had been estimated as 2%–3% of primary pediatric CNS tumors and 10% of infantile CNS tumors, with a slight male predominance (1.6:1.0)[7,8,14,15]. However, a study done in 2010 by Woehrer et al found that Atypical teratoid/rhabdoid tumors ranked as the sixth most common malignant CNS tumor[16].

Patients with AT/RT present with signs and symptoms that reflect the location of the tumor. Young patients with posterior fossa tumors usually present with symptoms related to hydrocephalus, namely early morning headaches, vomiting, and lethargy. They may also develop ataxia or

regression of motor skills. Because AT/RT is a highly malignant tumor, patients typically have a fairly short history of progressive symptoms measured in weeks. It is unusual for symptoms to have been present for more than a few months[17]. The current case was diagnosed in four years old boy who presented with symptoms of hydrocephalus and increase intracranial pressure associated with ataxia and disturbance of vision attributed to large posterior fossa tumor.

Imaging characteristics were nonspecific but helpful in identifying a possible AT/RT. However; CPA involvement and intratumoral hemorrhage are more common in atypical teratoid/rhabdoid tumor[18]. On MRI, the tumor mass was typically isointense and hyperintense foci secondary to intratumoral hemorrhage, necrosis, and cystic components. The CT appearance was typical of a hyperdense mass that enhances intensely with contrast[19].

The striking heterogeneity of the atypical teratoid/rhabdoid tumor shown by imaging studies reflects the histopathologic complexity of this tumor. Therefore awareness of atypical teratoid/rhabdoid tumor is important in making the correct diagnosis of this uncommon but probably underdiagnosed entity[20]. However, in our case the radiological report was heterogeneously enhancing solid and cystic posterior fossa tumor with hydrocephalus.

Atypical teratoid/rhabdoid tumor is recognized as a distinct clinical entity because of its pathologic and genetic characteristics. Histologically, AT/RT contains sheets of rhabdoid cells against a background of primitive neuroectodermal cells, mesenchymal cells, or epithelial components. Some tumors are composed almost entirely of rhabdoid cells (round nucleus with prominent nucleolus and abundant cytoplasm) while others show a combination of rhabdoid cells and areas resembling primitive neuroectodermal tumor or medulloblastoma[8,21,22].

Almost all the posterior fossa AT/RT cases described in the largest two series, which included 100 patients, were initially diagnosed as primitive neuroectodermal tumor[6,9]. This confusion is related to the fact that, only a minority of atypical teratoid/rhabdoid tumors has predominance of typical rhabdoid cells (the histologic hallmark of atypical teratoid/rhabdoid tumor), whereas 60%-70% of atypical teratoid/rhabdoid tumors contain fields indistinguishable from primitive neuroectodermal tumor[15,19].

Monosomy 22 or deletions of chromosome 22q11.2 result in alterations/inactivation of the hSNF5/ INI1 gene in somatic or in germ-line are commonly identified in patients with atypical teratoid/rhabdoid tumors of central nervous system as well as renal and extrarenal rhabdoid malignancies[9,11,23-26]. INI1 is a tumor suppressor gene which encodes ubiquitously expressed protein participates in chromatin remodeling, so mutation of this gene results in altered transcriptional regulation of cellular genes[27]. It is believed that the presence of an INI1 mutation in a tumor with histologic features suggestive of primitive neuroectodermal tumor without a clear rhabdoid component is sufficient to establish a diagnosis of AT/RT[28].

Treatment of AT/RT has often paralleled that of infant medulloblastoma or primitive neuroectodermal tumor. Most patients have received some form of multimodality therapy. AT/RT is a deadly disease, with initial retrospective studies reporting a time course from diagnosis to death of about 12 months with standard therapy[4,9].

Even after surgery and chemotherapy, the survival rate for children younger than 3 is less than 10 percent. While older children, treated with chemotherapy and radiation therapy after surgery, do somewhat better long-term, nearing 70 percent[29,30]. Furthermore results of other prospective study demonstrated a 2-year progression-free survival of 53% ± 13% and an overall survival of 70% ± 10%, with results most favorable in children who had had gross total resection and no metastatic disease at presentation[31].

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