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· 临床研究 ·

颅内原发性胚胎性癌的临床特征及预后影响因素分析*

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摘要 目的:探讨颅内原发性胚胎性癌的临床特征及预后影响因素,为该病的临床诊治提供参考依据。**方法:**回顾性分析我院经病理证实的6例颅内原发性胚胎性癌患者的临床资料,随访并比较患者的预后情况。**结果:**本组病例5例男性和1例女性,平均年龄9.8岁;5例病变位于松果体区,1例位于鞍区;5例头痛起病,1例表现为多尿;术前血液学检查提示:4例患者甲胎蛋白明显升高,1例患者β亚单位绒毛膜促性腺激素明显升高;3例患者手术全切,平均生存期32.0月,3例患者手术次全切,平均生存期21.0月;4例患者术后接受规范放化疗,平均生存期32.0月,1例仅行化疗,生存期22.0月,1例术后未行放化疗,生存期9.0月。**结论:**颅内原发性胚胎性癌是一种罕见的颅内肿瘤,多见于年轻男性,病变多位于松果体区;术前血液学检查有助于诊断;患者预后差,手术切除程度是一重要预后影响因素,术后放化疗或可延长患者的生存期。

关键词:颅内胚胎性癌;生殖细胞肿瘤;肿瘤标记物;预后

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Clinical Characteristics and Prognosis of Primary Intracranial Embryonal Carcinoma*

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ABSTRACT Objective: To analyze the clinical features and prognostic factors of intracranial primary embryonal carcinoma (EC), and provide references for the clinical diagnosis and treatment of EC. **Methods:** The clinical data of 6 cases of EC confirmed by pathology in our hospital were retrospectively analyzed and the prognosis was followed up and compared. **Results:** Of the 6 patients, 5 patients were males and 1 was female, their mean age was 9.8 years old. The lesions of 5 patients were in the pineal region and 1 in the sellar region. Of the 6 patients, 5 patients presented with headache and 1 presented with diuresis. Highly elevated alpha fetoprotein and beta subunit human chorionic gonadotropin were recorded in 4 and 1 patients' blood, respectively. The mean overall survival time for EC with total resection was 32.0 months. The mean overall survival time for EC with subtotal resection was 21.0 months. The mean overall survival time of the 4 patients undergoing standardized adjuvant chemoradiotherapy was 32.0 months. The survival time of one patient just undergoing chemotherapy was 22.0 months. The survival time of one patient without adjuvant therapy was 9.0 months. **Conclusion:** EC is a rare subtype of intracranial germ cell tumors with a tendency to present in younger patients and has a male bias, mostly located in the pineal region and has a poor prognosis. Preoperative hematologic examination is helpful for the diagnosis of EC. The extent of resection maybe is an important prognosis factor. Postoperative chemoradiotherapy might help prolong survival time.

Key words: Intracranial embryonal carcinoma; Germ cell tumor; Tumor marker; Prognosis

Chinese Library Classification (CLC): R739.4; R651.14 **Document code:** A

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前言

颅内生殖细胞肿瘤(Germ Cell Tumors, GCTs)是一类来源于原始胚胎生殖细胞较为罕见的肿瘤,主要发生于儿童和青少年^[1,2]。2016年,世界卫生组织(World Health Organization, WHO)将颅内GCTs分为7个亚型,发病率最高的是生殖细胞瘤,畸

胎瘤(未成熟、成熟)、畸胎瘤恶性转化、胚胎性癌(Embryonal Carcinoma, EC)、卵黄囊瘤、绒毛膜癌及混合型生殖细胞瘤相对少见^[3]。颅内原发性EC是一种罕见的颅内GCTs,只占颅内GCTs的1.8~5.0%^[4],目前对颅内EC的临床诊断、治疗和预后认识非常有限,鲜有文献报道。本研究回顾性分析2005年1月至2014年12月我院经手术病理证实的6例颅内原发性EC

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患者的临床资料并对其手术标本重新统一染色观察,以期为临床诊治提供参考。

1 材料与方法

表 1 6 例颅内原发性 EC 患者的临床资料

Table 1 Clinical data of 6 patients with intracranial primary EC

Patient	Sex	Age (years)	Location	Tumor diameter (mm)	Symptom	Degree of resection	Adjunctive therapy	Overall survival (months)
1	Male	2.2	Pineal region	18	Headache	Total resection	Chemotherapy	22.0
2	Female	9.5	Pineal region	21	Headache	Subtotal resection	Radiotherapy + chemotherapy	35.0
3	Male	18.9	Saddle area	37	Polyuria	Subtotal resection	Radiotherapy + chemotherapy	28.0
4	Male	6.2	Pineal region	32	Headache	Subtotal resection	None	9.0
5	Male	13.6	Pineal region	23	Headache	Total resection	Radiotherapy + chemotherapy	39.0
6	Male	8.4	Pineal region	19	Headache	Subtotal resection	Radiotherapy + chemotherapy	26.0

1.2 影像学、病理学资料

6 例患者术前均行头颅 MRI 检查,4 例行头颅 CT 平扫。所有标本均用 10%福尔马林缓冲液固定,常规处理,石蜡包埋,常规 HE 染色。各种抗体分别按以下稀释比例对所有标本进行免疫组织化学染色:CD30(1:100),胎盘碱性磷酸酶(placental alkaline phosphatase, PLAP)(1:100),甲胎蛋白(alpha fetoprotein, AFP)(1:100), β 亚单位绒毛膜促性腺激素(beta sub-unit human chorionic gonadotropin, β -HCG)(1:100)和 Ki-67(1:100),2 位经验丰富的神经病理学家对病理资料进行判读并依据 2016 年 WHO 中枢神经系统肿瘤分类做出病理分析^[2]。

1.3 治疗

6 例患者均行手术治疗,4 例存在脑积水患者入院后行脑室-腹腔分流术,待颅高压症状缓解后行手术治疗,5 例病变位于松果体区患者经枕部小脑幕入路切除肿瘤,1 例病变位于鞍区患者经双额底入路切除肿瘤,无手术死亡病例。术后患者接受辅助放疗($n=4$)和/或化疗($n=5$),由于 1 例患儿在首次手术时未满 36 月,考虑到放疗对大脑和脊髓的副作用未进行放疗,1 例因肿瘤短期内复发及经济原因,家属选择放弃治疗。患者术后四周接受同步放化疗,放疗方案包括足够范围总剂量为 50Gy 的局部放疗方案(2Gy/日,5 周);化疗方案为卡铂、异环磷酰胺及依托泊苷,每次化疗间隔 1.0~1.5 月,共 4~6 疗程。

1.4 统计学分析

采用 SPSS 22.0 软件进行数据统计分析,计量资料组间比较采用 t 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 影像学检查结果

5 例患者病变位于松果体区,1 例位于鞍区,病变呈类圆形($n=4$)或不规则($n=2$),4 例病变边界清楚,2 例病变边界不清,肿瘤 T1 加权像呈等信号($n=2$)或低信号($n=4$),T2 加权成像呈等信号($n=2$)或高信号($n=4$),增强扫描呈明显均匀($n=2$)或不均匀

1.1 临床资料

该组病例包括 5 例男性和 1 例女性,平均年龄 9.8 岁;5 例患者头痛起病,1 例表现为多尿;5 例位于松果体区,1 例位于鞍区,6 例患者临床资料见表 1。

($n=4$)强化,4 例患者表现为脑室扩大;4 例患者术前行 CT 平扫,CT 平扫呈等密度($n=2$)或稍高密度肿块($n=4$),2 例出现钙化,典型病例的影像图像见图 1。

2.2 血液学和病理学检查结果

4 例患者术前血液学检查提示 AFP 明显升高,1 例患者 β -HCG 明显升高。病理学检查提示肿瘤细胞比较大,细胞排列成乳头状;瘤细胞胞浆丰富,核大,空泡状,核仁大,异型性明显,核分裂活跃,肿瘤细胞提示较高的 Ki-67 增殖指数(60%~90%),血清肿瘤标记物检测结果显示和所有的免疫组化结果见表 2 和图 2。

2.3 预后

6 例患者均定期随访,随访时间 3~42 月。6 例患者都复发并且死于 ES,平均生存期 26.5 月。全切患者平均生存期为 32.0 月,次全切患者平均生存期为 21.0 月;另外,AFP 正常患者平均生存期为 37.0 月,AFP 升高患者平均生存期为 21.3 月;4 例术后接受规范放化疗患者的平均生存期为 32.0 月;1 例术后仅接受化疗,生存期为 22.0 月;1 例未行术后放化疗患者的生存期为 9.0 月。

3 讨论

EC 是一种罕见的颅内 GCTs 亚型,未有文献对其临床特征、诊断、影像、病理、治疗及其预后进行系统总结。目前,临床对 EC 的临床特征、影像学特点、治疗方案及预后等认识不足,诊断和治疗选择也是根据颅内常见 GCTs 的特点制定。由于不同组织学亚型颅内 GCTs 的生物学特性、治疗方法及其预后差别很大,因而阐明 EC 的临床特点对于制定更有针对性的治疗策略以改善预后至关重要。

颅内 GCTs 好发于儿童和青少年,绝大多数分布在松果体区和鞍上^[1,2],部分多部位起源,基底节及小脑也是较常见的部位;另外,男女比例与肿瘤部位、组织学类型有关,成熟畸胎瘤好发于女性,而未成熟畸胎瘤没有性别差异。据文献报道,松果

体区和基底节 GCTs 主要发生于男性,而鞍区 GCTs 女性稍占优势^[45]。在本组病例中,EC 患者确诊的平均年龄 9.8 岁,男女比例 5:1,激素水平差异可能有助于解释 EC 的性别差异,5 例位于松果体区,1 例位于鞍区。

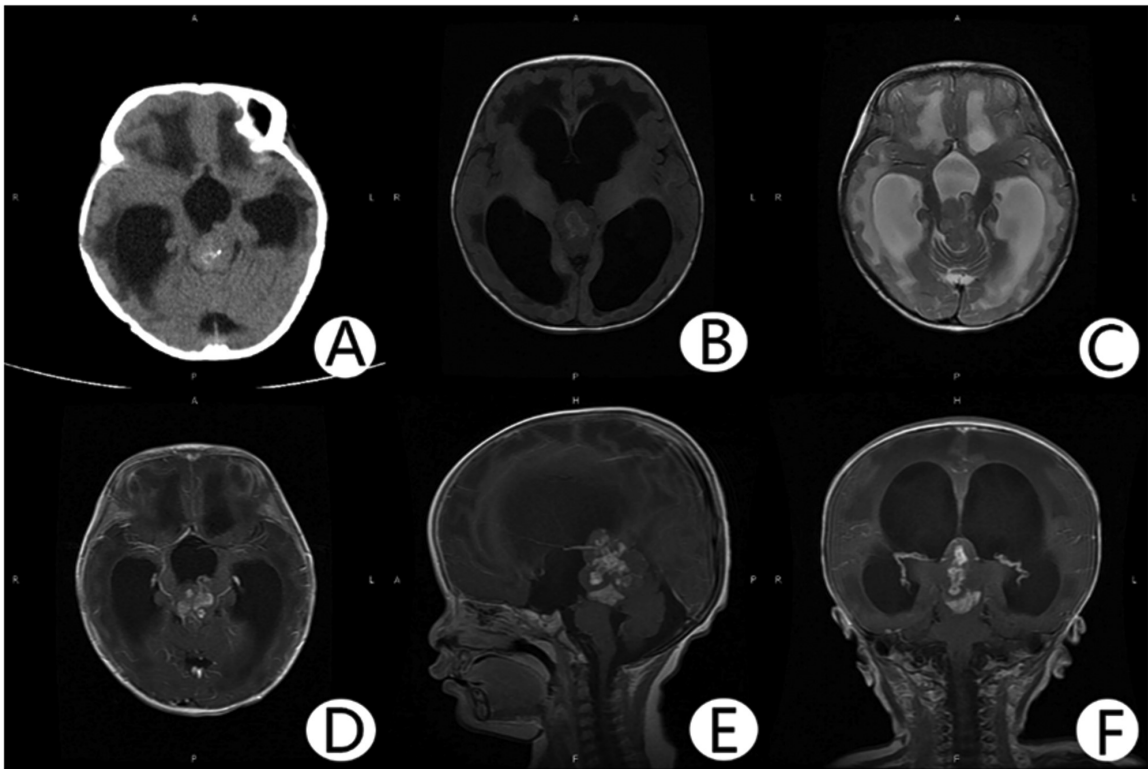


图 1 1 例典型 EC 患者的影像学表现

Fig.1 Imaging findings of a typical EC patient

Note: A: Head CT scan showed nodular high-density lesions in the pineal region, and spotted calcification was observed in the lesion; B: The axial T1 weighted image is dominated by a low signal, and a small piece of slightly higher signal is visible inside C: Axis T2 weighted image is a mixed signal; D-F: Enhanced MRI shows uneven enhancement of lesions

表 2 6 例颅内原发性 EC 的血液肿瘤标记物及免疫组织化学特点

Table 2 Tumor markers in blood and immunohistochemical features of 6 cases with intracranial primary EC

Patient	Tumor marker in Blood		Immunohistochemical staining				
	AFP	β-HCG	AFP	β-HCG	CD30	PLAP	Ki-67
1	+	-	+	+	-	+	60
2	-	-	-	-	+	-	60
3	+	-	-	-	+	-	90
4	+	+	+	+	-	+	90
5	-	-	-	-	+	-	80
6	+	-	+	+	-	+	70

Note: AFP (+): ≥ 12 ng/mL; AFP (-): < 12 ng/mL; β-HCG (+): ≥ 5 mIU/mL; β-HCG (-): < 5 mIU/mL.

不同组织学亚型颅内 GCTs 的临床症状和体征没有明显特异性,颅内 GCTs 的临床症状与肿瘤位置和大小有关。眼部症状和梗阻性脑积水所致颅高压症状通常是常见的首发症状,由于阻塞中脑导水管引起脑积水和压迫中脑顶盖,大部分松果体区 GCTs 患者表现为颅高压症状、复视及 Parinaud 综合征;由于压迫或侵袭视交叉,鞍上 GCTs 患者多表现为尿崩症、闭经及视力减退^[6]。本组病例结果显示 EC 的发病部位和相应的临床症状与文献关于颅内 GCTs 的报道基本一致。本研究中,松果体区 EC 患者主要表现为颅高压症状,鞍区 EC 患者表现为多尿,合并梗阻性脑积水的松果体区 GCTs 患者常需行引流

术或脑室造瘘术^[7],松果体区 EC 患者为缓解梗阻性脑积水行脑室腹腔分流术。

肿瘤标志物在颅内 GCTs 诊治中发挥重要作用,最常见的标志物是 AFP 和 β-HCG^[8-10]。肿瘤标志物的水平与预后有关,AFP 升高的患者提示预后差。Kim 等人的研究显示 AFP 和 β-HCG 升高的 GCTs 患者预后差^[11]。在本组病例中,血清 AFP 升高对于诊断 ES 有一定的提示作用,AFP 正常患者平均生存期为 37.0 月,AFP 升高患者平均生存期为 21.3 月,AFP 升高提示患者预后更差。

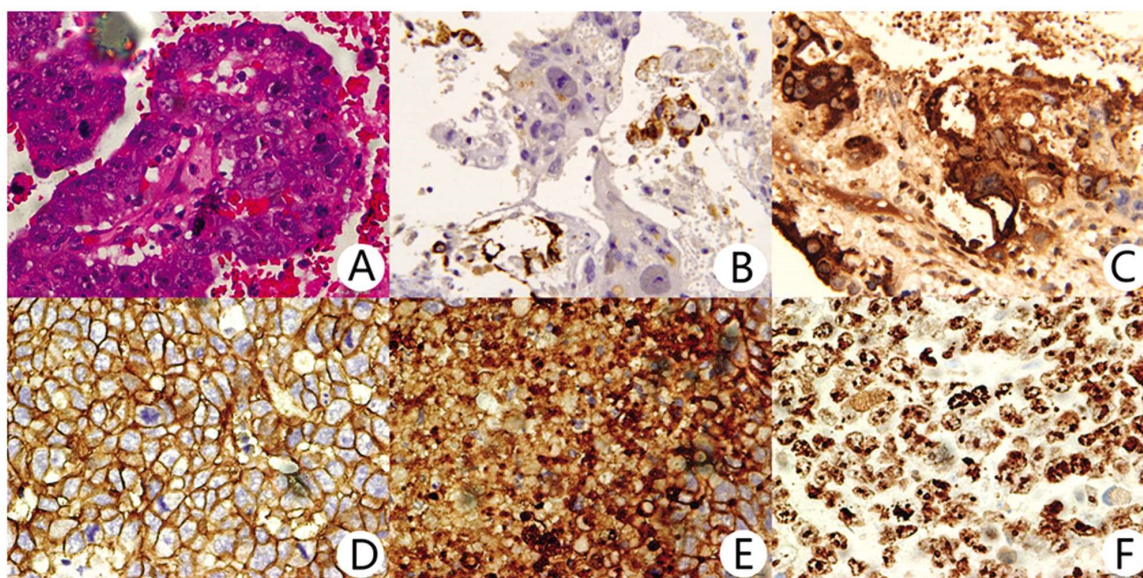


图 2 EC 患者术后 HE 染色和免疫组织化学染色结果(× 400)

Fig.2 Postoperative HE staining and immunohistochemical staining results in patients with EC(× 400)

Note: A: HE; B: AFP; C:β-HCG; D: PLAP; E: CD30; F: Ki-67.

颅内 GCTs 在影像学上无典型特点^[12,13], 本研究中大部分病例显示肿瘤边界较清, 肿瘤内部密度 / 信号不均匀、增强后明显不均匀强化, 可能与肿瘤内钙化、坏死有关, 与 EC 恶性程度高、生长迅速特点相符。仅依据 CT 和 MRI 资料以鉴别 EC 与其他亚型颅内 GCTs 异常困难^[14], 但将 CT、MRI 结果与年龄、性别、初始症状、部位及血清学标志等临床资料相结合有助于在术前预测肿瘤亚型^[15]。

恶性颅内 GCTs 患者的 3 年生存率为 27.3 %^[16,17]。本研究中, EC 患者的平均生存期为 26.5 月, 预后差^[18]。恶性非生殖细胞瘤的生殖细胞肿瘤的治疗包括切除肿瘤控制局部肿瘤细胞, 放疗覆盖脑膜扩散的肿瘤细胞, 化疗清除全身播散的肿瘤细胞^[19-22]。通常认为切除范围是许多肿瘤最重要的预后因素之一, 非生殖细胞瘤的生殖细胞肿瘤患者的生存率与肿瘤切除程度显著相关^[23-25]。在本研究中, 全切患者平均生存期 32.0 月, 次全切患者平均生存期 21.0 月, 全切患者生存时间明显多于次全切患者。目前, EC 的最佳治疗方案尚无共识, 术后辅助放化疗对于提高生存质量和生存期有重要作用^[26-30]。本组病例中, 术后接受规范辅助放化疗患者的平均生存期为 32.0 月, 只接受化疗患者的生存期为 22.0 月, 其中 1 例患者未进行放化疗短期内复发并死亡, 提示术后放化疗对延长 EC 患者生存期有重要意义。

总之, 颅内原发性胚胎性癌是一种罕见的颅内生殖细胞肿瘤亚型, 预后差, 多见于年轻男性, 病变多位于松果体区; 术前血液学检查有助于术前诊断; 对于怀疑胚胎性癌的患者, 目前主要的治疗方案主要包括手术切除局部病灶和术后放化疗以延长生存期, 手术切除范围是一重要预后影响因素。

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