·临床病理报告·

脂肪样星形细胞瘤

温爽 王辅林

【摘要】 **目的** 探讨脂肪样星形细胞瘤的临床病理学特征、免疫表型、诊断与鉴别诊断、治疗及预后。**方法与结果** 男性患者,48岁。临床表现为左手无名指及小指麻木、活动不利。MRI显示右顶叶占位性病变,伴囊性变,实性区域明显强化。立体定向下行右顶叶肿瘤全切除术。光学显微镜观察肿瘤呈低级别星形细胞瘤形态,散在一些胞质丰富、核仁明显的神经元样细胞;以脂肪空泡形成为特征,形似成熟的脂肪细胞,呈灶状相互融合,似微囊性变。肿瘤细胞表达胶质纤维酸性蛋白、S-100蛋白、WT-1蛋白和少突胶质细胞转录因子2,以及神经元标志物突触素、微管相关蛋白-2、神经微丝蛋白、神经元特异性烯醇化酶和CD34,不表达异柠檬酸脱氢酶1,P53蛋白呈弱阳性(5%),Ki-67抗原标记指数约为1%。术后随访20个月,肿瘤无复发。**结论** 脂肪样星形细胞瘤为临床少见肿瘤,组织病理学呈低级别星形细胞瘤形态,伴显著脂肪样细胞分化,亦可伴神经元样分化。明确诊断需结合病理学形态及免疫表型,同时应注意与其他伴脂肪样细胞分化或黄色瘤样变的神经上皮组织肿瘤相鉴别。

【关键词】 星形细胞瘤; 脂细胞; 神经元; 免疫组织化学; 病理学

Clinicopathological features of cerebral lipoastrocytoma

WEN Shuang, WANG Fu-lin

Department of Pathology, Chinese PLA General Hospital, Beijing 100853, China

Corresponding author: WANG Fu-lin (Email: wfl301@gmail.com)

【**Abstract**】 **Objective** To explore the clinicopathological features, immune phenotype, diagnosis and differential diagnosis, treatment and prognosis of cerebral lipoastrocytoma. **Methods** Retrospective analysis of the clinical manifestations, histopathological and immunohistochemical features were conducted in one case of cerebral lipoastrocytoma. **Results** A 48-year-old male presented with numbness and inflexibility of the fourth and little fingers of his left hand over the previous 2 weeks. Cranial MRI revealed a space-occupying lesion with cystic degeneration in the right parietal lobe that showed obvious enhancement after contrast administration. The patient subsequently underwent craniotomy with stereotactic gross total excision of the lesion. Adjuvant chemotherapy and radiation therapy were not administered. Histologically the tumor showed classical features of low-grade astrocytoma, including a few scattered medium-large neuron-like cells with prominent nucleoli and abundant cytoplasm. Most notably, the glial cells contained fat droplets or vacuoles giving an appearance of mature adipocytes. Focally microcystic change was evident resulting from adipocyte-like cells fusion with each other. Immunohistochemically, the tumor cells were reactive for glial fibrillary acidic protein (GFAP) and S-100 protein (S-100), focally positive for WT-1, weakly positive for oligodendrocytes transcription factor-2 (Olig-2), and negative for isocitrate dehydrogenase 1 (IDH1). Meanwhile, the tumor cells also expressed several neuronal markers including synaptophysin (Syn), microtube-associated protein-2 (MAP-2), neurofilament (NF), neuron specific enolase (NSE) and CD34. P53 protein was weakly expressed in 5% of tumor cells. Ki-67 labeling index was low (1%). The patient remained well without recurrence 20 months after surgery. **Conclusions** Cerebral lipoastrocytoma is an extremely rare tumor. Histologically, the tumor showed classical features of low-grade astrocytoma and extensive lipomatous differentiation. Interestingly, the present case also showed neuronal differentiation confirmed by positive staining with neuronal markers. Diagnosis needs to be combined with pathological morphology and immune phenotype, which can distinguish from other neuroepithelial tumors with fat cell differentiation or xanthomatous change.

【**Key words**】 Astrocytoma; Adipocytes; Neurons; Immunohistochemistry; Pathology

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作者单位:100853 北京,解放军总医院病理科[温爽(现在辽宁省大连市友谊医院病理科,邮政编码:116100)]

通讯作者:王辅林(Email:wfl301@gmail.com)

中枢神经系统神经上皮组织肿瘤[1]中黄色瘤样变与脂肪瘤样变(亦称脂肪样细胞分化)组织形态学表现不同,前者脂质以多发脂肪滴空泡形式聚积于肿瘤细胞胞质内,类似黄色瘤样,如多形性黄色瘤型星形细胞瘤[2-3]和脂质化胶质母细胞瘤[4-7];后者则表现为脂肪滴在肿瘤细胞胞质内凝聚成单个透亮空泡,推挤胞核至胞质边缘,形似成熟的脂肪细胞,多见于室管膜瘤[8-9]、低级别星形细胞瘤[10-12]、小脑的神经元与神经胶质混合性肿瘤[13-14]和中枢神经细胞瘤[15-17]。脂肪样星形细胞瘤是一种极为少见的低级别星形细胞瘤[13],其病理学特征为星形细胞瘤肿瘤组织中伴脂肪样细胞分化。笔者报告1例颅内脂肪样星形细胞瘤患者的临床诊断与治疗经过,并结合文献对其临床和影像学表现、组织病理学及免疫表型特征进行分析。

病历摘要

患者　男性,48岁。主诉左手不适2周,于2011年11月11日入院。患者入院前2周无明显诱因出现左手无名指和小指麻木、活动不利,于当地医院行头部MRI检查显示右顶叶占位性病变,遂至我院就诊。病程中无头痛、头晕,无恶心、呕吐,无肢体抽搐、意识丧失,精神、食欲及睡眠良好,无大小便障碍。既往高血压病史2年,口服抗高血压药物可控制。无其他疾病,家族史及个人史无特殊。

诊断与治疗经过　体温36.8℃,脉搏78次/min,呼吸18次/min,血压160/97 mm Hg(1 mm Hg = 0.133 kPa)。体格检查意识清楚,一般状态良好。内科系统及神经系统查体无异常。头部MRI检查显示右顶叶实性占位性病变伴水肿,病灶中心微囊性变;增强扫描病灶实性区明显强化(图1)。临床诊断:右顶叶占位性病变。入院后第4天于全身麻醉立体定向下实施右顶叶占位性病变切除术。术中可见皮质下1 cm病变区,显微镜下病灶呈暗灰色、胶冻状、质地柔软、血供丰富;留取标本后吸引器吸出病变组织至正常脑组织边界。术后行组织病理学检查。(1)大体标本观察:手术切除标本为黄色碎组织块,大小约1.00 cm × 0.70 cm × 0.50 cm,质地柔软。标本经质量分数为10%中性甲醛溶液固定、石蜡包埋、常规切片并HE染色。(2)组织形态学观察:肿瘤细胞密度中等、大小不一,具有多形性,伴嗜酸性胞质,呈纤维性星形细胞样分化;胞核不规则,呈卵圆形、杆状或多角形,未见核分裂象;可见散在单核和多核巨细胞,胞质丰富,伴显著核仁及核内包涵体(INIs),似神经元样分化。典型病理学特征为肿瘤细胞内有大量脂肪空泡形成,部分填充胞质,推挤胞核至胞质边缘,形似成熟的脂肪细胞;局灶区域脂肪样细胞呈灶状相互融合,似微囊性变;肿瘤组织中未见坏死、血管内皮增生、Rosenthal纤维、嗜酸性颗粒及钙化(图2)。(3)免疫组织化学染色(SP二步法):胶质纤维酸性蛋白(GFAP)、S-100蛋白(S-100)、异柠檬酸脱氢酶1(IDH1)、WT-1蛋白(WT-1)、少突胶质细胞转录因子2(Olig-2)、突触素(Syn)、微管相关蛋白-2(MAP-2)、神经微丝蛋白(NF)、CD34、神经元特异性烯醇化酶(NSE)、P53和Ki-67抗原均购自北京中杉金桥生物技术有限公司。操作步骤严格按照试剂盒说明书进行,以相应部位着色呈均匀一致棕色颗粒为染色成功标准。结果显示,肿瘤细胞表达GFAP(图3a)、S-100(图3b)、Olig-2(图3c)和WT-1,不表达IDH1;同时表达神经元标志物Syn(图3d)、MAP-2(图3e)、CD34(图3f)、NSE(图3g)和NF;P53蛋白阳性率为5%(图3h),Ki-67抗原标记指数为1%。病理诊断:(右顶叶)脂肪样星形细胞瘤。术后患者病情平稳,未诉特殊不适,头部切口愈合良好,术后8 d出院。术后未辅助放射治疗和药物化疗,电话随访20个月,肿瘤无复发。

讨　论

本文病例免疫组织化学染色显示肿瘤细胞表达GFAP,伴显著脂质化细胞,其形态与成熟脂肪细胞相似。中枢神经系统肿瘤细胞脂质化是肿瘤化生的一种类型,其原因尚不十分清楚。有观点认为,是神经外胚层细胞的真性脂肪化生,但这些脂质化肿瘤细胞表达神经胶质细胞免疫表型(GFAP和S-100),因此并非真正的脂肪化生过程[18]。原始神经外胚层肿瘤脂质化可能是肿瘤细胞去分化、代谢异常或变性的结果[19]。

CT可显示脂肪瘤样改变[12]。Giangaspero等[10]报告2例患者,1例额叶肿瘤表现为与其他低级别肿瘤(如毛细胞型星形细胞瘤、节细胞胶质瘤、多形性黄色瘤型星形细胞瘤)相似的影像学特征,呈大囊腔伴小附壁瘤结节;增强扫描瘤结节明显强化;另1例左颞枕叶肿瘤呈T_1WI高信号,误诊为脂肪

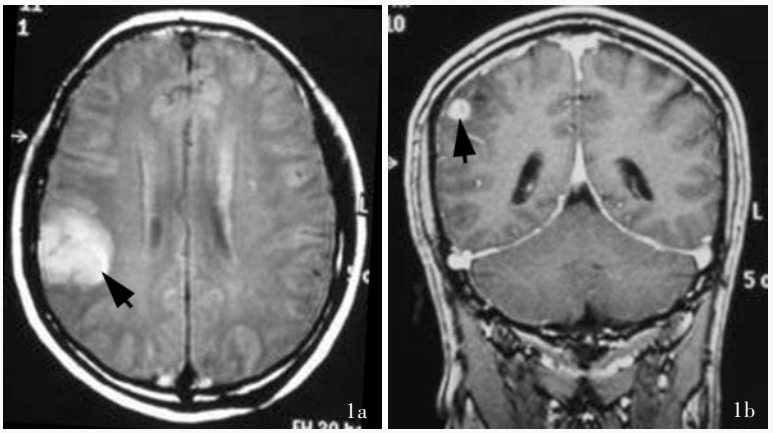

图1　头部MRI检查所见　1a　横断面FLAIR成像显示，右顶叶实性占位性病变，呈不均匀高信号，病灶中心呈微囊性变，周围水肿呈高信号（箭头所示）　1b　冠状位增强T_1WI显示，病灶实性区呈不均匀强化（箭头所示），周围水肿明显，呈低信号

Figure 1　Cranial MRI findings. Axial FLAIR demonstrated a solid lesion in the right parietal lobe. The lesion showed heterogeneous hyperintense signal with microcystic change in center and hyperintense edema around the lesion (arrow indicates, Panel 1a). Coronal enhanced T_1WI showed prominent heterogeneous enhancement of the solid part (arrow indicates) and hypointense edema around the lesion (Panel 1b).

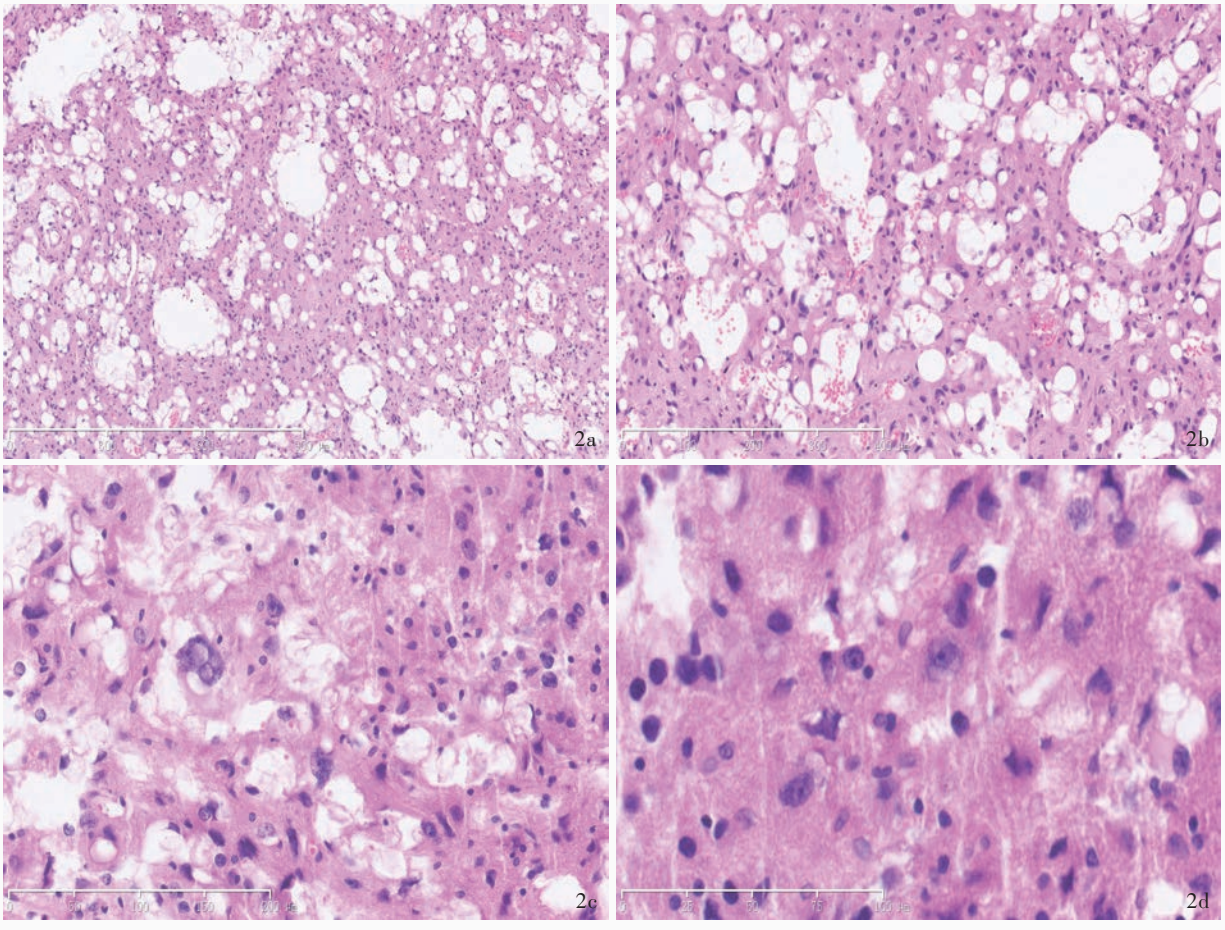

图2　光学显微镜观察所见　HE染色　2a　肿瘤组织由大小不一的肿瘤细胞及较大的脂肪样细胞组成，伴微囊性变　×5　2b　肿瘤细胞密度中等，胞核不规则，呈卵圆形或杆状，脂肪样细胞呈空泡状，推挤胞核至胞质边缘　×10　2c　可见单核及多核巨细胞，胞核呈空泡状，似核内包涵体　×20　2d　少数肿瘤细胞体积较大，胞核呈圆形或卵圆形，染色质细腻，伴显著嗜酸性核仁，似神经元样分化　×40

Figure 2　Optical microscopy findings. HE staining　A mixture of astrocytes with varied sizes and large adipocyte-like cells with microcystic degeneration were noted in tumor (Panel 2a).　×5　Diffuse infiltration by medium cellularity of astrocytes with irregular shape of nuclei (oval or rod-shaped) and vacuolate adipocytes with peripheral displacement of the nucleus were demonstrated in tumor (Panel 2b).　×10　Mononuclear or multinuclear giant cells with vesicular nucleus similar to intranuclear inclusions were easily seen (Panel 2c).　×20　A few large tumor cells with round to oval nuclei containing fine granular chromatin and prominent eosinophilic nucleoli, similar to neuronal differentiation, were also identified (Panel 2d).　×40

瘤，表明肿瘤富含脂肪成分，其脂肪成分在T_1WI上呈高信号，与皮下脂肪信号相似。磁共振波谱成像（MRS）对检测少量脂肪组织敏感，可证实存在脂质峰，而常规影像学检查发现脂肪信号则需与畸胎

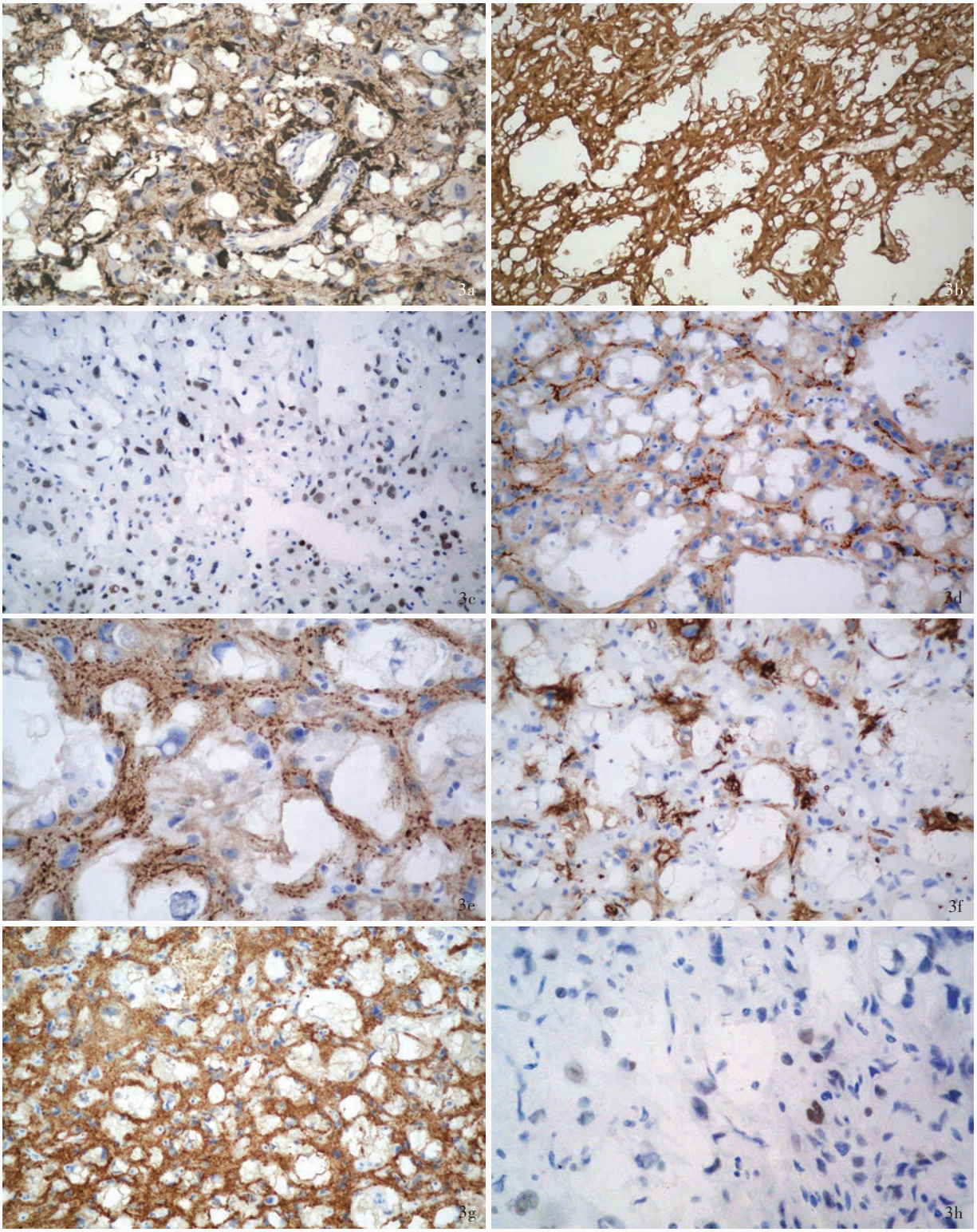

图3　光学显微镜观察所见　免疫组织化学染色(SP二步法)　3a　肿瘤细胞GFAP表达阳性　×200　3b　肿瘤细胞S-100表达阳性　×200　3c　肿瘤细胞胞核Olig-2阳性表达率为30%～50%　×100　3d　肿瘤细胞Syn表达阳性　×200　3e　肿瘤细胞MAP-2表达阳性　×400　3f　神经元样肿瘤细胞CD34表达阳性　×200　3g　肿瘤细胞NSE表达阳性　×100　3h　肿瘤细胞胞核P53阳性表达率约为5%　×200

Figure 3　Optical microscopy findings.　Immunohistochemical staining (SP)　The neoplasm cells were positive for GFAP (Panel 3a) and S-100 (Panel 3b).　×200　The positive rate of Olig-2 in the nuclei of tumor cells was about 30%–50% (Panel 3c).　×100　The neoplasm cells were positive for Syn (Panel 3d).　×200　The neoplasm cells were positive for MAP-2 (Panel 3e).　×400　CD34 positive staining was found in some neuron-like cells (Panel 3f).　×200　Tumor cells were positive for NSE (Panel 3g).　×100　P53 protein was expressed in about 5% of tumor cells (Panel 3h).　×200

瘤、皮样囊肿等肿瘤相鉴别[20]。

脂肪样星形细胞瘤细胞密度中等、大小不一，部分呈梭形伴嗜酸性胞质和纤维凸起，为神经胶质细胞分化特征，呈浸润性生长；肿瘤细胞胞核不规则，呈卵圆形或杆状，染色质略浓染，核仁不明显，无核分裂象。无坏死和血管内皮增生，表现为低级别星形细胞瘤的组织病理学特征。脂肪样细胞弥漫性分布于肿瘤细胞间，呈圆形或多角形，胞核受脂质空泡推挤而呈偏心状，位于胞质一侧边缘，形似成熟的印戒样脂肪细胞，可见局灶性钙化[19-20]。本文患者于显微镜下可见胞质丰富的单核及多核巨细胞，伴显著核仁及核内包涵体；免疫组织化学染色支持肿瘤细胞伴神经元样分化特征。

明确诊断需结合影像学、组织病理学和免疫组织化学，并应与下列疾病相鉴别。(1)脂肪神经细胞瘤：为好发于成人小脑的肿瘤，也可见于幕上[15,17]，后者称为中枢性或幕上脂肪神经细胞瘤，可伴神经元样和脂肪样分化。其脂肪样细胞分布与脂肪样星形细胞瘤相似，二者易混淆。本文病例因首次免疫组织化学染色呈局灶性弱阳性表达GFAP、阳性表达神经元标志物(如MAP-2、CD34、Syn)而诊断为脂肪样神经细胞瘤。脂肪样细胞间的脂肪神经细胞瘤细胞大小相对一致、胞核规则，与中枢神经细胞瘤相似，免疫表型呈神经元标记，不表达GFAP；而脂肪样星形细胞瘤细胞呈星形细胞样分化，伴嗜酸性胞质，胞核不规则，GFAP表达阳性。此外，由于肿瘤常见于大脑皮质浅层，须谨慎辨认正常残留的神经元成分，以免误认为肿瘤性成分。(2)多形性黄色瘤型星形细胞瘤：好发于青少年，主要位于大脑皮质浅层，光学显微镜观察肿瘤性星形细胞呈多形性为其主要特征，表现为纤维性、单核或多核巨细胞形态，部分肿瘤细胞富含脂肪滴，形似黄色瘤样[2-3]。除了肿瘤性黄色瘤样细胞表达GFAP，部分肿瘤细胞还表达神经元标志物，且伴明显的血管周围淋巴细胞浸润和致密的网状纤维反应，可资与脂肪样星形细胞瘤相鉴别。(3)脂质化室管膜瘤：任何年龄均可发病，好发于脑室。光学显微镜下观察肿瘤细胞呈中等密度，形态较一致，可伴较显著的脂质化细胞[8-9]。但肿瘤组织内可见特征性血管周围“假菊形团”样或室管膜“菊形团”样结构，免疫组织化学染色肿瘤细胞胞质呈“逗点(dot-like)”样表达上皮膜抗原(EMA)；而脂肪样星形细胞瘤无血管周围“假菊形团”样或室管膜“菊形团”样结构，也不表达EMA。(4)富脂质髓母细胞瘤：可见于成人[21-23]，位于幕下。肿瘤组织由高密度肿瘤细胞和脂肪样细胞组成，肿瘤细胞大小相对一致，胞质淡染、弱嗜酸性，胞核呈圆形或卵圆形，染色质细腻，核分裂象易见；脂肪样细胞为圆形或多边形，呈空泡状，单个或成片排列于肿瘤细胞间。肿瘤细胞和脂肪样细胞同时表达神经元标志物(Syn、NSE)，以及GFAP和S-100[22,24]，Ki-67抗原标记指数为15%～40%[25-26]。虽然二者发生部位相互重叠，可见于第四脑室[27]和脑桥小脑角[19]，但光学显微镜下脂肪样星形细胞瘤细胞大小不甚一致，呈梭形或细长，嗜酸性胞质显著，伴肥胖型星形细胞，胞核不规则，呈卵圆形或短梭形，染色质致密，核仁不明显，核分裂象罕见；肿瘤细胞弥漫表达GFAP，一般不表达神经元标志物。

目前，对于脂肪样星形细胞瘤的治疗仍以外科手术切除为主，无需放射治疗或药物化疗。对术后辅助性放射治疗和药物化疗效果尚存争议，且无长期获益证据，对于复发或残留病灶进展的病例，仍适用于外科手术切除[28]。

鉴于脂肪样星形细胞瘤病例数较少、随访时间较短，长期预后尚不十分明确。脂肪样星形细胞瘤常见于伴毛细胞型星形细胞特征的肿瘤，而毛细胞型星形细胞瘤为WHO Ⅰ级肿瘤，故预后良好[5]。笔者对11例脂肪样星形细胞瘤患者的临床病理学特征进行总结(文献10例[10-12,19-20,27-30]、本文1例，表1)。结果显示，该肿瘤可见于不同年龄、解剖部位、肿瘤分级及亚型；发病年龄为2～77岁(平均为30.60岁)，男性7例、女性4例；主要分布于大脑皮质(5例)、脊髓(2例)、小脑(2例)、第四脑室(1例)和脑桥(1例)；肿瘤大多界限清楚，呈外生性生长，可有包膜(脊髓部位)或局限性生长，仅1例呈弥漫性生长；肿瘤全切除8例(其中1例肿瘤复发而再次手术切除)，次全切除2例(其中1例同时辅以放射治疗和药物化疗)，1例脑桥肿瘤患儿未行手术而仅接受放射治疗和药物化疗；其中6例伴毛细胞型星形细胞瘤特点(双相组织学排列、Rosenthal纤维和嗜酸性颗粒小体)、4例呈纤维性星形细胞特点、1例为低级别肿瘤；随访9个月至7年，多数预后良好，无复发，其中2例随访3～7年，2例带瘤生存且病情稳定，1例脑桥肿瘤明确诊断后8个月死亡。本文病例为中年男性，右顶叶脂肪样星形细胞瘤，肿瘤全

表1 11例脂肪样星形细胞瘤患者临床病理学特征

Table 1. Clinicopathological features of 11 cases with lipoastrocytoma

Case	Source	Sex	Age (year)	Location	Pathological feature	Treatment	Prognosis
1	Giangaspero, et al [10] (2002)	Female	2	Left temporal-occipital	Well-circumscribed, pilocytic feature	Total removal	3 years, no recurrence
						Re-excision 28 months after initial surgery	
2	Giangaspero, et al [10] (2002)	Male	12	Left frontal	Well-circumscribed, cystic, mural nodule, pilocytic feature	Total removal	7 years, no recurrence
3	Roda, et al [11] (1995)	Female	48	Spinal cord, multiple, intramedullary	Incomplete capsule, pilocytic feature	Total removal	2 years, no recurrence
4	Walter, et al [12] (1994)	Female	77	Left cerebellum	5 cm, local, pilocytic feature	Subtotal removal	9 months, stable
5	Gheri, et al [19] (2010)	Male	39	Cerebellum, pons, extramedullary	exophytic, glial fibrillary	Total removal	10 months, residual tumor
6	Craver, et al [20] (2012)	Male	7	Pons	Diffuse pattern, glial fibrillary	Radiotherapy, chemotherapy	Died 8 months after diagnosis
7	Lee, et al [27] (2009)	Male	32	Fourth ventricle	Well-circumscribed, pilocytic feature	Total removal	< 1 year, no recurrence
8	Aryan, et al [28] (2003)	Female	36	T_{9-11} spinal cord, intramedullary	Well-circumscribed, bi-phasic pattern, glial fibrillary	Total removal	1 year, no recurrence
9	Ramírez-Aguilar, et al [29] (2007)	Male	24	Right temporal	Well-circumscribed, glial fibrillary	Total removal	5 years, no recurrence
10	Massimi, et al [30] (2010)	Male	12	Left frontal	Well-circumscribed, low-grade	Radiotherapy, chemotherapy, total removal	2 years, no recurrence
11	The present (2013)	Male	48	Right parietal	Well-circumscribed, glial fibrillary	Total removal	20 months, no recurrence

切除后未行放射治疗和药物化疗，随访20个月，肿瘤无复发，目前仍在随访中。

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·小词典·

中英文对照名词词汇(四)

神经微丝蛋白 neurofilament protein(NF)
神经炎性斑 neuritic plaque(NP)
[老年斑 senile plaque(SP)]
神经元特异性烯醇化酶 neuron specific enolase(NSE)
神经原纤维缠结 neurofibrillary tangles(NFTs)
时间飞跃 time-of-flight(TOF)
收缩期峰值流速 peak systolic velocity(PSV)
舒张期末流速 end diastolic velocity(EDV)
髓周动-静脉瘘 perimedullary arteriovenous fistula(PAVF)
锁骨下动脉盗血综合征 subclavian steal syndrome(SSS)
梯度回波序列 gradient echo sequence(GRE)
体感诱发电位 somatosensory-evoked potentials(SEPs)
微管相关蛋白-2 microtubule-associated protein-2(MAP-2)
无症状性颈动脉外科手术试验
Asymptomatic Carotid Surgery Trial(ACST)
无症状性颈动脉粥样硬化研究
Asymptomatic Carotid Atherosclerosis Study(ACAS)
下颌骨角 angle of mandible(AM)
相对各向异性 relative anisotropy(RA)
信噪比 signal-to-noise ratio(SNR)
星状神经节阻滞 stellate ganglion block(SGB)
选择性部分反转恢复
selective partial inversion recovery(SPIR)
血管内皮生长因子
vascular endothelial growth factor(VEGF)
血友病 Willebrand disease(WD)
烟雾病 moyamoya disease(MMD)
异柠檬酸脱氢酶1 isocitrate dehydrogenase 1(IDH1)
婴儿促纤维增生性星形细胞瘤
desmoplastic infantile astrocytoma(DIA)
硬脑膜动-静脉瘘 dural arteriovenous fistula(DAVF)
Glasgow预后分级 Glasgow Outcome Score(GOS)
运动诱发电位 motor-evoked potentials(MEPs)
症状性重度颈动脉狭窄患者内膜切除术与支架成形术研究
Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis(EVA-3S)
支架和强化药物治疗预防颅内动脉狭窄患者脑卒中复发研究
Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)
Barthel指数 Barthel Index(BI)
质子密度加权像 proton density weighted image(PDWI)