

易误诊的化生型脑膜瘤

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【摘要】 目的 化生型脑膜瘤临床少见,对其临床表现和组织病理学特征进行探讨,并复习相关文献,避免误诊。**方法与结果** 女性患者,17岁,彝族。临床表现为突发性头痛、呕吐、发热伴四肢抽搐。头部CT显示右侧额顶叶不规则低密度影,边界欠清晰,其内含类钙化高密度影,大小约2 cm×1.80 cm×1.70 cm;MRI可见右侧额顶叶大小约2.40 cm×2.10 cm×2 cm的肿瘤影,周围脑组织大片状水肿。术中于右侧额顶叶脑实质内见一占位性病变,一侧紧邻软脑膜,未侵及硬脑膜和颅骨,形状不规则,边界较清晰,表面血供丰富,呈黄色、质地较硬,大小约3 cm×2.50 cm×2 cm。光学显微镜观察肿瘤组织广泛骨化和钙化,肿瘤细胞呈片状和小巢状分布在网状排列的小梁状骨组织间;肿瘤细胞表达上皮膜抗原、孕激素受体、波形蛋白和Bcl-2,Ki-67抗原标记指数约为6%。**结论** 化生型脑膜瘤的化生成分多种多样,其影像学也存在多样性,通过组织形态学和免疫组织化学可明确诊断,并与其化生成分相似的肿瘤进行鉴别,以免误诊。

【关键词】 脑膜瘤; 化生; 免疫组织化学; 病理学

Easily misdiagnosed metaplastic meningioma: one case report and review of literature

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【Abstract】 Objective Metaplastic meningioma is rare lesion which is very difficult to diagnose clinically, and is easy to be misdiagnosed. This article aims to reveal the clinical manifestations and histopathological features of this disease. **Methods** One case of ossification metaplastic meningioma was reported and the relevant literatures were reviewed. **Results** A 17-year-old female patient showed paroxysmal stiffness accompanied by convulsion of extremities, headache, vomiting and fever. Cranial CT scan demonstrated an irregular low-density signal in the right frontal and parietal lobes. The lesion did not have a clear boundary, and there was a calcificated high-density signal inside it. The size of the lesion was about 2 cm×1.80 cm×1.70 cm. Cranial MRI scan showed a tumor with size of 2.40 cm×2.10 cm×2 cm, located in the right frontal and parietal lobes, and there was large edema around the lesion. A resection was performed, and a lesion was found in the right frontal and parietal parenchyma, whose one side was close to the cerebral pia mater and did not invade into the dura and the skull. The tumor was yellow, in irregular shape, and had clear boundary, with hard texture and rich blood supply. Its size was about 3 cm×2.50 cm×2 cm. There was extensive ossification and calcification within the tumor under microscope. Tumor cells were flaky and like small nests, which were distributed in the mesh-like arranged trabecular bone. The immunohistochemical staining showed that epithelial membrane antigen (EMA), progesterone receptor (PR), vimentin (Vim) and Bcl-2 were positive for tumor cells with Ki-67 labeling index being about 6%. **Conclusions** Metaplastic meningioma has various metaplastic components and its imaging features are also various. However, it could be diagnosed and identified from other similar tumors by histopathological observation and immunohistochemical staining.

【Key words】 Meningioma; Metaplasia; Immunohistochemistry; Pathology

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化生型脑膜瘤(metaplastic meningioma)临床较为少见,本文报告1例误诊为骨母细胞瘤的化生型脑膜瘤患者,并对其临床表现、影像学和组织病理学特征进行回顾分析,以探讨该病的诊断与鉴别诊断要点。

病历摘要

患者 女性,17岁,彝族。主因突发性头痛、呕吐、发热伴四肢抽搐,于2011年8月11日入院。患者入院前37h突发全头部胀痛,频繁喷射状呕吐后出现四肢抽搐、口吐白沫、双眼向上凝视、小便失禁,伴短暂性意识丧失数分钟,发作后全身大汗淋漓、四肢无力、高热(41.1℃)。经当地医院治疗后症状未见明显好转,逐渐出现左上肢肌无力,头部CT检查显示右侧额顶叶占位性病变,遂转至攀枝花学院附属医院神经外科进一步治疗。患者自发病以来精神、食欲、睡眠尚可,大小便正常,体重无明显变化。

既往史、个人史及家族史 患者平素身体健康,无不良嗜好,否认肝炎、结核病等传染病病史,否认药物过敏史,否认高血压、糖尿病、心脏病病史,以及外伤或手术史。无家族遗传性疾病病史。

体格检查 患者体温39.3℃,呼吸19次/min,脉搏115次/min,血压101/68 mm Hg(1 mm Hg = 0.133 kPa)。发育正常,急性痛苦面容,精神萎靡,查体合作。全身皮肤黏膜无黄染,浅表淋巴结无肿大。头部、五官无畸形,气管居中,甲状腺未扪及肿大。心界正常、心律齐,各瓣膜听诊区未闻及病理性杂音,胸廓未见异常;双肺叩诊呈清音,呼吸音清,未闻及干湿啰音和胸膜摩擦音。腹部外形正常,全腹部柔软,肝脾无肿大,肾区无叩痛。神经科专科检查:神志清楚,Glasgow昏迷量表(GCS)评分为15分。双侧瞳孔等大、等圆,约为3.50 mm,对光反射灵敏,双眼活动正常。双耳闻及弹指声,伸舌居中。颈部稍抵抗,左上肢肌力4级、肌张力不高,其余肢体活动度良好,肌力5级、肌张力正常。双侧腹壁反射正常,双侧膝腱反射正常。双侧病理征未引出。

辅助检查 入院后完善各项实验室检查,血液一般检查与物理性质,以及肝肾功能试验均无异常。腰椎穿刺脑脊液外观无色透明,常规、生化均于正常值范围。头部CT显示右侧额顶叶不规则低密度影,边界欠清晰,其内可见类钙化高密度影,大

小约为2 cm×1.80 cm×1.70 cm,各脑室、脑池形态、大小正常,中线结构无偏移(图1)。头部MRI显示右侧额顶叶大小约2.40 cm×2.10 cm×2 cm的稍长T₁、短T₂信号影,FLAIR成像和扩散加权成像(DWI)呈低信号;增强后病灶呈轻度不均匀强化,病灶周围可见大片水肿区;脑室系统无扩大,中线结构居中(图2)。

诊断与治疗经过 综合患者临床表现及入院前后各项检查结果,临床诊断考虑为右侧额顶叶占位性病变,继发癫痫发作。经对症支持治疗病情稳定后,于全身麻醉下行右侧额顶叶占位性病变切除术。术中可见病灶位于右侧额顶叶脑实质内,一侧紧邻软脑膜,未侵及硬脑膜和颅骨,形状不规则,边界较清晰,表面血供丰富,呈黄色,质地坚硬,大小约3 cm×2.50 cm×2 cm。手术全切除病灶,并行组织病理学检查。(1)大体标本观察:手术切除标本呈灰白色不规则组织块,大小约3 cm×2.50 cm×2 cm,质地较硬,切面呈砂砾感。经体积分数为4%的中性甲醛溶液固定,常规脱水、透明、石蜡包埋制备脑组织切片,分别行HE染色和免疫组织化学染色。(2)HE染色:光学显微镜观察显示,肿瘤组织内大量骨组织和钙化区域,大部分骨组织呈网状,由随意排列、大小不等的小梁状骨组织构成,亦可见较大块的骨组织和钙化区域;骨组织间可见肿瘤细胞呈片状、小巢状排列和分布;肿瘤细胞呈短梭形或卵圆形,胞核卵圆形,核仁可见,胞质红染或略透明,细胞大小较为一致,核异型性不明显,未见病理性核分裂象;肿瘤细胞间未见明确的纤维间质,间质内血管清楚,部分区域可见少量脂肪组织;肿瘤组织边界清楚,与周围脑组织形成“推挤式”边界,周围脑组织水肿明显(图3)。(3)超微结构观察:于HE染色观察定位下获取组织,二甲苯脱蜡、二甲苯和树脂1:1比例浸透、树脂聚合包埋,行常规电子显微镜切片染色,HITACHI H7650型透射电子显微镜(日本HITACHI公司)观察。肿瘤细胞呈短梭形或卵圆形,胞质内可见粗面内质网和部分微丝,细胞间连接较为密切,可见桥粒样结构,偶见胶原纤维(图4)。(4)免疫组织化学染色(EnVision二步法):所用I抗、II抗、显色剂、染色系统参见表1。结果显示,肿瘤细胞上皮膜抗原(EMA)、孕激素受体(PR)、波形蛋白(Vim)和Bcl-2表达阳性;内皮细胞标志物CD34、CD99、广谱细胞角蛋白(PCK)、胶质纤维酸性蛋白(GFAP)、少突胶质细胞转录因子2

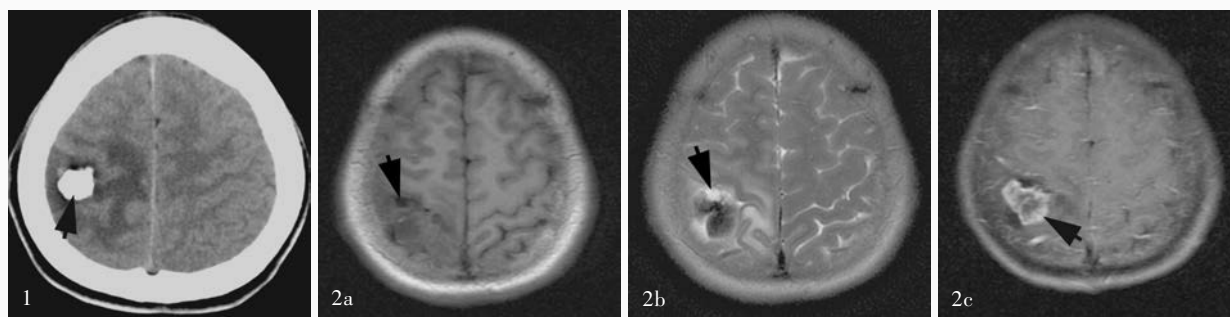


图1 头部CT检查显示,右侧额顶叶交界区不规则低密度影,边界欠清晰,其内含类钙化高密度影(箭头所示) 图2 头部MRI检查所见 2a 横断面T₁WI显示右侧额顶叶交界区大小约2.40 cm×2.10 cm×2 cm略低信号影(箭头所示) 2b 横断面T₂WI显示病灶呈低信号(箭头所示) 2c 横断面增强T₁WI显示病灶呈轻度不均匀强化(箭头所示),周围大片状水肿区

Figure 1 Cranial CT findings. An irregular low-density signal was found in the junction of right frontal and parietal lobes. The lesion did not have a clear boundary, and there was a calcificated high-density signal inside it (arrow indicates). **Figure 2** Cranial MRI findings. Axial T₁WI showed a low-intensity lesion with the size of about 2.40 cm×2.10 cm×2 cm located in the junction of right frontal and parietal lobes (arrow indicates, Panel 2a). Axial T₂WI showed a low-intensity lesion (arrow indicates, Panel 2b). Axial enhanced T₁WI showed the lesion was mild heterogeneous enhancement (arrow indicates) and there was large edema around the lesion (Panel 2c).

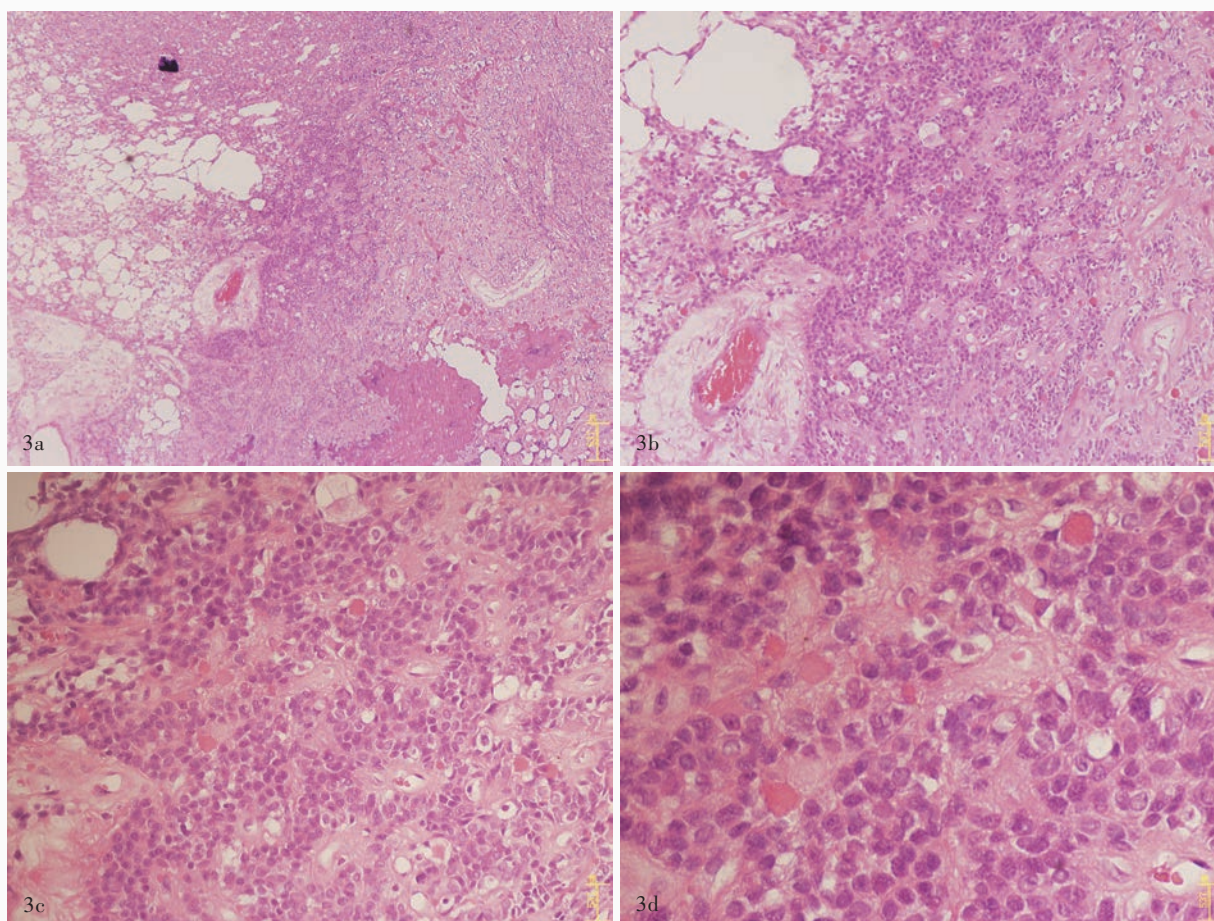


图3 光学显微镜观察所见 HE染色 3a 可见较大的骨化区域和呈网状排列的大小不等的小梁状骨化,亦可可见少量脂肪化生 ×20 3b 肿瘤细胞呈片状和小巢状分布在呈网状的小梁状骨组织之间 ×50 3c 肿瘤细胞呈短梭形,胞核卵圆形,胞质红染或略透明,细胞大小较一致,核异型性不明显 ×100 3d 肿瘤细胞呈短梭形,胞核卵圆形,胞质红染或略透明,细胞大小较一致,核异型性不明显 ×200

Figure 3 Optical microscopy findings. HE staining There was large ossification area and trabecular ossification ranging in random size. There was also a small amount of fat metaplasia (Panel 3a). ×20 Tumor cells were flaky and like small nests, which were distributed in the mesh-like trabecular bone (Panel 3b). ×50 The tumor cells were short spindle in shape with oval nuclei, and the cytoplasm was stained red or slightly transparent. The cells also had uniform size without atypia (Panel 3c). ×100 The tumor cells were short spindle in shape with oval nuclei, and the cytoplasm was stained red or slightly transparent. The cells also had uniform size without nuclear atypia (Panel 3d). ×200

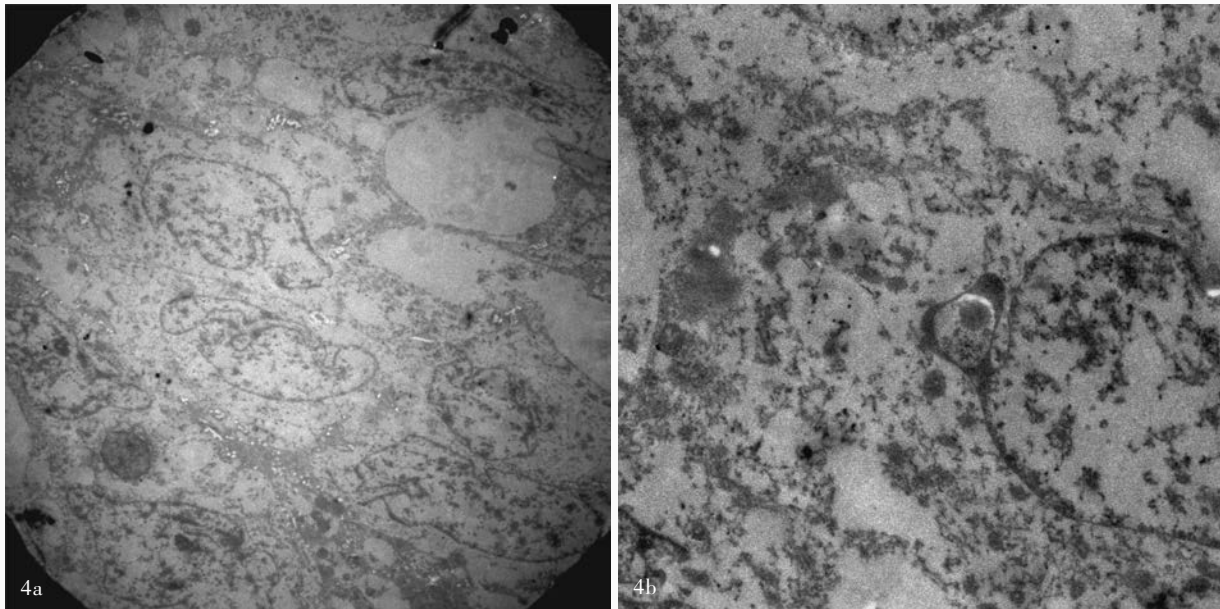


图4 透射电子显微镜观察所见 枸橼酸铅、醋酸铀双重染色 4a 肿瘤细胞呈短梭形或卵圆形,胞质内可见粗面内质网和部分微丝,肿瘤细胞间连接紧密,并可见桥粒样结构,偶见胶原纤维 $\times 700$ 4b 肿瘤细胞呈短梭形或卵圆形,肿瘤细胞间连接密切,可见桥粒样结构 $\times 2500$

Figure 4 Transmission electron microscopy findings. Lead citrate and uranyl acetate double staining Tumor cells were short spindle or oval in shape. In the cytoplasm rough endoplasmic reticulum and a little part of microfilaments could also be seen. Tumor cells were more closely connected, and desmosomes-like structure were visible, with accidental collagen fiber filaments (Panel 4a). $\times 700$ Tumor cells were short spindle or oval in shape, more closely connected and visible desmosomes-like structure (Panel 4b). $\times 2500$

表1 免疫组织化学检测项目表

Table 1. Antibodies used for immunohistochemical examination

Antibody I	Clone ID	Company	Restorative procedure	Dilution ratio	Antibody II company	Dyeing system
EMA	E29	Dako (Denmark)	Citric acid	1 : 150	Dako (America)	EnVision
PR	1E2	Roche (Switzerland)	EDTA	Ready-to-use	Roche (Switzerland)	EnVision
Vim	V9	Dako (Denmark)	Citric acid	1 : 200	Dako (Denmark)	EnVision
Bcl-2	124	Dako (Denmark)	Citric acid	1 : 200	Dako (Denmark)	EliVision
Ki-67	EP5	Zhongshan (China)	EDTA	1 : 500	Maixin (China)	EnVision
CD34	QBEnd 10	Dako (Denmark)	Citric acid	1 : 150	Dako (Denmark)	EnVision
CD99	12E7	Dako (Denmark)	Citric acid	1 : 100	Dako (Denmark)	EnVision
GFAP	—	Dako (Denmark)	Citric acid	1 : 10 000	Dako (Denmark)	EnVision
PCK	AE1/AE3	Zhongshan (China)	Citric acid	1 : 200	Dako (Denmark)	EnVision
Olig-2	EP112	Zhongshan (China)	EDTA	Ready-to-use	Dako (Denmark)	EnVision
S-100	Kit-0007-2	Maixin (China)	Citric acid	1 : 100	Maixin (China)	Maixin (China)

—, polyclonal antibody, 多克隆抗体; EMA, epithelial membrane antigen, 上皮膜抗原; PR, progesterone receptor, 孕激素受体; Vim, vimentin, 波形蛋白; GFAP, glial fibrillary acidic protein, 胶质纤维酸性蛋白; PCK, pan cytokeratin, 广谱细胞角蛋白; Olig-2, oligodendrocytes transcription factor-2, 少突胶质细胞转录因子-2; S-100, S-100 protein, S-100蛋白; EDTA, ethylenediaminetetraacetic acid, 乙二胺四乙酸

(Olig-2)表达阴性;少许细胞S-100蛋白(S-100)表达阳性, Ki-67抗原标记指数约为6%(图5)。病理诊断:右侧额顶叶化生型脑膜瘤(WHO I级)。术后患者生命体征平稳, 15 d后痊愈出院。3个月后复查CT, 肿瘤无复发, 随访至今已2年余, 未见肿瘤复发。

讨 论

脑膜瘤是中枢神经系统常见肿瘤之一, 由脑膜皮细胞构成, 起源于蛛网膜颗粒细胞的内皮细胞和纤维母细胞, 最常发生在颅内, 多与硬脑膜关系密

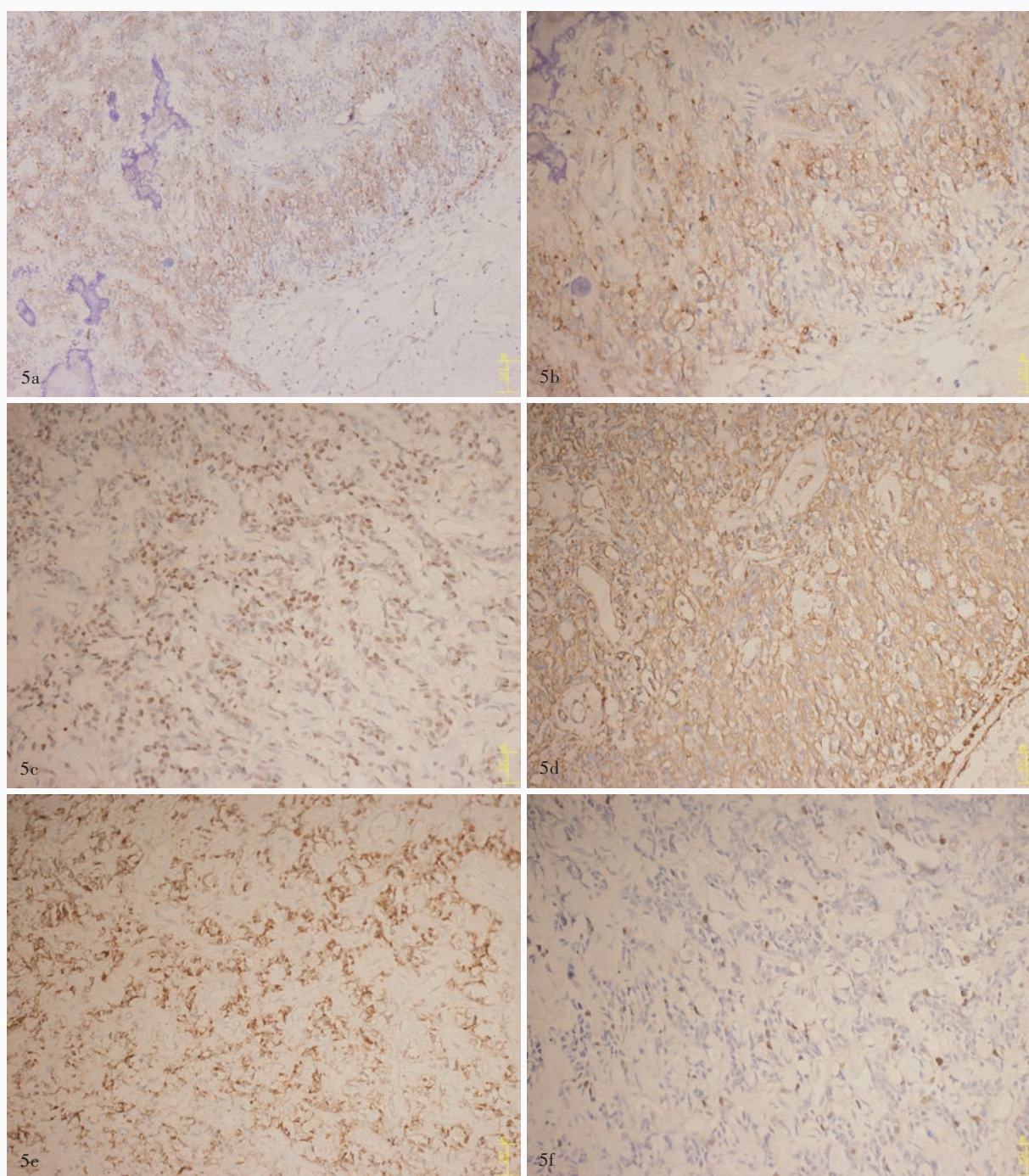


图 5 光学显微镜观察所见 免疫组织化学染色(EnVision 二步法) 5a 肿瘤细胞 EMA 表达阳性 × 50 5b 肿瘤细胞 EMA 表达阳性 × 100 5c 肿瘤细胞 PR 表达阳性 × 100 5d 肿瘤细胞 Vim 表达阳性 × 100 5e 肿瘤细胞 Bcl-2 表达阳性 × 100 5f 肿瘤细胞 Ki-67 抗原标记指数约为 6% × 100

Figure 5 Optical microscopy findings. Immunohistochemical staining (EnVision) EMA was positive for tumor cells (Panel 5a). × 50 EMA was positive for tumor cells (Panel 5b). × 100 PR was positive for tumor cells (Panel 5c). × 100 Vim was positive for tumor cells (Panel 5d). × 100 Bcl-2 was positive for tumor cells (Panel 5e). × 100 Ki-67 labeling index was about 6% (Panel 5f). × 100

切,亦可发生于椎管,椎管内脑膜瘤相对少见,占椎管内肿瘤的 15.50%^[1]。脑膜瘤多见于成人,特别是中老年人,女性好发,而儿童和青少年少见,但其发

生的脑膜瘤侵袭性更强。世界卫生组织将脑膜瘤分为 WHO I ~ III 级,大多数为 WHO I 级。脑膜瘤组织形态学多样,可以分为多种亚型,每种亚型的

复发和进展各不相同,化生型脑膜瘤是其中一种少见亚型,属WHO I级,为具有间叶组织分化的脑膜瘤,可见骨、软骨、脂肪、黏液或黄色瘤样细胞等间叶组织成分,但其临床意义尚不清楚。

化生型脑膜瘤的临床表现与其他类型一样,与肿瘤位置密切相关,临床主要表现为头痛、眩晕和癫痫发作^[2]。大多数患者出现症状就诊时,均可在影像学上发现肿瘤影像,常规CT和MRI有助于诊断,MRI表现为等信号,部分钙化,增强后病灶可强化,由于化生的成分不同,其在T₁WI和T₂WI上信号不同,部分T₁WI呈低信号,部分T₂WI呈低信号^[2]。其化生成分中以骨化生和脂肪化生最为常见^[2-6],也可有黏液样、平滑肌和黄色瘤样化生^[7-8]。有文献报道,“脂肪化生”这一定义用于某些进行性黄色瘤样变并不恰当,其非特异性胞质脂肪样变并非真正的化生,建议改用“脂肪瘤样脑膜瘤”^[5-6]。也有文献报道,化生型脑膜瘤可有多种成分,在诊断时应仔细查找其中有无恶性程度更高的成分,例如骨组织化生型脑膜瘤应注意是否有横纹肌样型脑膜瘤成分,因为横纹肌样型脑膜瘤同样可以出现骨化生,但其横纹肌样成分更突出,为恶性程度较高的类型(WHO III级)^[9]。该例患者化生成分为大量骨化生和钙化区域,部分区域可见少量脂肪化生,未见其他恶性程度更高的成分。

该例患者组织病理学观察显示肿瘤组织广泛骨化和钙化,骨化区域大部分表现为随意排列的大小不等的网状小梁状骨组织,亦可见较大的骨化和钙化区域;肿瘤细胞呈片状和小巢状分布在网状排列的小梁状骨组织间,肿瘤细胞呈短梭形,胞核卵圆形,胞质红染或略透明,细胞大小较一致,核异型性不明显,未见病理性核分裂象;间质内血管丰富,扩张充血;部分区域可见少量脂肪化生,肿瘤边界较清楚,与周围脑组织形成“推挤式”边界,周围脑组织水肿明显。该例患者曾被某国外医院的病理医师诊断为骨母细胞瘤。我们结合其年龄、临床特点、神经影像学、组织学、超微结构和免疫组织化学染色结果,明确诊断为以骨组织为主的化生型脑膜瘤(WHO I级)。

骨组织化生型脑膜瘤应注意与以下疾病相鉴别。(1)骨母细胞瘤:好发于脊柱和长管状骨,皮质和骨膜下少见,多发生于10~30岁,男性好发。组织学特点除编织状针样骨样基质和骨组织外,最突出的特征是肿瘤组织散在分布的破骨细胞型多核

巨细胞,骨组织间为骨母细胞,分化良好,沿骨样基质边缘排列。该例患者未见沿骨样基质排列的细胞成分,亦未见多核巨细胞,仅见呈短梭形的片状和小巢状肿瘤细胞分布在小梁状骨组织间,可资鉴别。(2)骨瘤:好发于颅骨和面骨,成年男性多发,通常无症状,被认为是骨的错构瘤,一般情况下无需治疗^[10]。其组织学形态由成熟的较宽的小梁状骨组织构成,排列不规则,其间有纤维、血管和脂肪等组织,有时可见造血细胞。该例患者组织学表现为小梁状骨组织间呈片状和小巢状排列的短梭形肿瘤细胞,胞核卵圆形,胞质红染或略透明,未见造血细胞。影像学易将骨组织化生型脑膜瘤误诊为骨母细胞瘤和骨瘤,但组织形态学和免疫组织化学易于鉴别。(3)颅内钙化性假瘤(亦称纤维-骨化性损害):一种极为罕见的瘤样病变。其组织学形态可见成熟的板层状骨质和灶状钙盐沉着,钙化成分间可见梭形细胞,部分区域呈“栅栏”状排列,细胞间有黏液样间质成分;其梭形细胞类似脑膜上皮细胞,但不表达EMA,可资与骨组织化生型脑膜瘤相鉴别,且肿瘤周围可见组织细胞和多核巨细胞形成的肉芽肿^[11-12]。(4)脑室外神经细胞瘤(EVN):较为少见,属WHO II级,多发生于20~40岁成年人,男女发病率基本相同。CT显示肿瘤钙化和囊性变,MRI呈等或高信号。肿瘤细胞形态单一,胞核圆形或卵圆形,组织学形态多样,可见“菊形团”结构和少突胶质细胞瘤样“蜂窝”状结构等,一般无小梁状骨组织。免疫组织化学神经细胞标志物表达阳性,可与骨组织化生型脑膜瘤相鉴别。(5)少突胶质细胞瘤:属WHO II级,好发于成人,40~50岁多见,多位于大脑半球白质内。CT显示肿瘤钙化,MRI显示长T₁、长T₂信号的边界清楚病灶,周围水肿不明显。肿瘤细胞中等密度,形态一致,胞核圆形,胞质透亮,可见核周空晕,肿瘤间可见“鸡爪”样丛状增生的毛细血管。免疫组织化学染色有助于鉴别。

化生型脑膜瘤预后较好,以外科手术为主,鉴于其复发可能性^[13],部分患者术后可适当予放射治疗。脑膜瘤的发病机制与NF-2基因突变有一定关系,同时有学者提出了与其发生有一定相关性的其他基因^[14-15],这将给对手术治疗和放射治疗均无明显效果的患者进行靶向治疗提供一定的研究方向。

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脑梗死急诊溶栓及神经保护新进展学习班通知

首都医科大学宣武医院拟定于 2014 年 9 月 3-5 日举办国家级继续医学教育项目“脑梗死急诊溶栓及神经保护新进展学习班[项目编号:2013-04-04-029(国)]”。学习班依托首都医科大学宣武医院在神经学科群的整体优势,紧密结合国际最新进展,在大量临床经验的基础上,对静脉溶栓、动脉溶栓、机械性取栓的选择和排除标准、技术操作、重症监护及超早期康复治疗等进行系统讲解和技术推广。学习结束后考核通过者将授予国家级继续医学教育学分 6 分。

1. 培训地点 首都医科大学宣武医院(北京市西城区长椿街 45 号)。
2. 培训对象 神经内科、神经外科、急诊科及相关专业中级职称及以上人员。
3. 教学内容 脑卒中急诊影像学评价、脑卒中急诊超声评价、急诊动脉溶栓治疗、急性缺血性卒中机械性血管内治疗、后循环进展性卒中血管内治疗、急性脑卒中神经保护治疗等。
4. 报名方式 请于 2014 年 8 月 20 日前发送报名回执至:wjxjy2014@163.com。联系人:高骅。联系电话:(010)83198952。

高血压及脑静脉病变诊治新进展学习班通知

首都医科大学宣武医院拟定于 2014 年 9 月 3-5 日举办北京市继续医学教育项目“高血压及脑静脉病变诊治新进展学习班[项目编号:2013-04-04-013(京)]”。学习班依托首都医科大学宣武医院在神经学科群的整体优势,紧密结合国际最新进展,在大量临床经验的基础上,对脑静脉疾病的诊断与鉴别诊断、治疗规范及神经介入放射学技术进行讲解。学习结束后考核通过者将授予市级继续医学教育学分 6 分。

1. 培训地点 首都医科大学宣武医院(北京市西城区长椿街 45 号)。
2. 培训对象 神经内科、神经外科及相关专业中级职称及以上人员。
3. 教学内容 颈静脉疾病的影像学及超声诊断,脑静脉窦血栓的鉴别诊断,脑静脉窦血栓的机械性血管内治疗,脑静脉窦血栓的转化医学研究等。
4. 报名方式 请于 2014 年 8 月 20 日前发送报名回执至:wjxjy2014@163.com。联系人:高骅。联系电话:(010)83198952。