

· 临床研究 ·

脑膜癌 23 例临床特点分析

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【摘要】目的 总结以神经系统症状首发的脑膜癌患者的临床特征。**方法** 收集2009年6月至2017年12月确诊为脑膜癌患者的临床资料,对其临床、实验室及影像学表现进行归纳分析。**结果** 86.96%(20/23)患者以头痛首发,52.17%(12/23)为头痛伴呕吐。MRI增强扫描病灶明显强化,59.09%(13/22)伴脑室系统扩大;CT表现为幕上脑室系统扩大(1例)。肿瘤原发灶主要源于肺癌,约占65.22%(15/23),其他来源为结肠癌、淋巴瘤、胃癌和星形细胞瘤(腰髓)各占4.35%(1/23),来源不详者占17.39%(4/23)。脑脊液压力明显升高者占82.61%(19/23);肿瘤标志物以癌胚抗原升高者较为多见,血清筛查为11/17例、脑脊液为7/10例。**结论** 脑膜癌临床症状以头痛伴呕吐常见;影像学检查主要表现为脑膜强化或伴交通性脑积水;实验室检查以颅内高压为特征性改变,血清和脑脊液肿瘤标志物癌胚抗原明显升高。原发灶主要来源于肺癌,脑脊液细胞学检出肿瘤细胞为诊断“金标准”。

【关键词】 脑膜肿瘤; 肿瘤转移; 磁共振成像; 生物标记,肿瘤

Clinical characteristics of 23 cases of meningeal carcinomatosis

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【Abstract】Objective To investigate the clinical characteristics of meningeal carcinomatosis with nervous system syndrome as initial symptom. **Methods** Clinical data, laboratory and imageing examinations were retrospectively analyzed in 23 patients of meningeal carcinomatosis from June 2009 to December 2017. **Results** Twenty patients (86.96%) had headache as initial symptom and 12 (52.17%) had headache with vomiting. Head enhanced MRI showed obvious enhancement in meningeal lesions, and 13 cases (59.09%) had meningeal enhancement with enlargement of ventricular system; CT showed enlargement of supratentorial ventricular system (1 case). About 65.22% (15/23) primary lesions were originated from lung cancer, and others were originated from colon cancer, hematological lymphoma, gastric cancer, spinal astrocytoma (4.35%, 1/23 respectively), and some unknown origin (17.39%, 4/23). About 82.61% (19/23) patients cerebrospinal fluid pressure increased obviously, Tumor markers especially carcinoembryonic antigen (CEA) were mostly increased in serum (11/17) and cerebrospinal fluid (7/10). **Conclusions** Headache and vomiting are the most common clinical symptoms of meningeal carcinomatosis. Enhanced MRI shows meningeal enhancement or communicating hydrocephalus. Cerebrospinal fluid pressure tends to increase significantly. Carcinoembryonic antigen is significantly increased in serum and cerebrospinal fluid. Primary lesions of meningeal carcinomatosis mostly originate from lung cancer. Finding tumor cells in cerebrospinal fluid is the "golden standard" of diagnosis.

【Key words】 Meningeal neoplasms; Neoplasm metastasis; Magnetic resonance imaging; Biomarkers, tumor

Conflicts of interest: none declared

脑膜癌又称为脑膜转移癌或癌性脑膜炎,是恶

性肿瘤的晚期严重并发症之一,患者预后不良。其临床表现缺乏特异性,易误诊或漏诊。为了探讨脑膜癌的临床特征,笔者拟对广东三九脑科医院神经内科近年诊断与治疗的23例脑膜癌患者的临床、实验室以及影像学检查结果进行总结分析,以供同行参考。

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对象与方法

一、病例选择

1. 诊断标准 (1)有明确的肿瘤病史。(2)临幊上有新近出现的神经系统症状与体征。(3)CT或MRI检查呈典型的脑膜强化并伴脑室扩大的影像学特征。(4)脑脊液细胞学检查发现肿瘤细胞。凡符合以上4项条件者即可确诊为脑膜癌。另外,对于一些有明确原发肿瘤病史,且影像学检查呈典型脑膜癌征象的病例,即使脑脊液细胞学检查未发现肿瘤细胞仍可诊断为脑膜癌。

2. 纳入与排除标准 (1)符合脑膜癌诊断标准。(2)腰椎穿刺脑脊液细胞学检测明确检出肿瘤细胞。(3)排除入院前经外院确诊并已接受过针对脑膜癌的综合治疗。(4)本研究经广东三九脑科医院道德伦理委员会审核批准,患者及其家属知情同意并签署知情同意书。

3. 一般资料 所有患者均为2009年6月至2017年12月在我院神经内科住院治疗并经脑脊液细胞学检测确诊的脑膜癌病例共23例,男性7例,女性16例,男女比例为1:2.29;年龄31~75岁,中位年龄54岁;发病至就诊时间为10天至6个月,中位病程2个月;出现症状至确诊时间为14天至6个月,其中15例(65.22%)于发病3个月内确诊。

二、临床特点

1. 症状与体征 本组患者主要表现为头痛、呕吐和视力下降,但无发热现象,大多数患者以头痛为主症(20例占86.96%),或头痛伴呕吐(12例占52.17%),亦可单纯表现为视力下降(10例占43.48%);余伴发症状有癫痫发作(6例占26.09%)、精神异常(5例占21.74%)、头晕和眩晕(5例占21.74%)、行走不稳(4例占17.39%)、视物重影(4例占17.39%)、记忆力减退(2例占8.70%)、听力下降(2例占8.70%)、眼睑下垂(2例占8.70%)、面部麻木(1例占4.35%),以及吞咽困难(1例占4.35%)。

2. 肿瘤原发部位 本组23例脑膜癌患者中有15例(65.22%)原发肿瘤源于肺[非小细胞肺癌(腺癌)13例、小细胞肺癌2例],结肠癌(腺癌)、胃癌(腺癌)、淋巴瘤[B细胞非霍奇金淋巴瘤(B-NHL)]和星形细胞瘤(腰髓,WHOⅡ级)各1例(4.35%),余4例(17.39%)肿瘤来源不详。

三、实验室检查

1. 血清学 17例(73.91%)行血清肿瘤标志物

筛查的患者中11例癌胚抗原(CEA)血清水平升高,其中同时伴有糖类抗原153(CA153)或CA199水平升高者各1例;原发肿瘤位于肺者9/11例,均为非小细胞肺癌(腺癌);结肠癌(腺癌)和原发灶不详者各1例。余6例肿瘤标志物筛查呈阴性,肺癌2例[非小细胞肺癌(腺癌)1例、小细胞肺癌1例]、B-NHL、星形细胞瘤(腰髓)1例、原发灶不详2例。

2. 脑脊液 (1)生化指标:本组患者均行脑脊液检查,有4例(17.39%)压力正常($80\sim180\text{ mm H}_2\text{O}$, $1\text{ mm H}_2\text{O} = 9.81 \times 10^{-3}\text{ kPa}$)、19例(82.61%)压力升高,其中11例(47.83%)压力 $>330\text{ mm H}_2\text{O}$;白细胞计数正常[(0~5) $\times 10^6/\text{L}$]或轻度升高;4例蛋白定量于正常值范围(150~450 mg/L)、19例(82.61%)升高,其中8例(34.78%)蛋白定量 $>1000\text{ mg/L}$;14例(60.87%)葡萄糖水平正常(2.50~4.40 mmol/L)、6例(26.09%)降低(最低0.20 mmol/L)、3例升高且血糖水平亦高于正常值范围(3.10~6.90 mmol/L);17例(73.91%)氯化物于正常值范围(120~130 mmol/L)、6例降低。(2)肿瘤标志物筛查:仅10例行脑脊液肿瘤标志物筛查,7例癌胚抗原脑脊液水平升高,其中6例为肺癌[均为非小细胞肺癌(腺癌)]、1例结肠癌(腺癌);3例肿瘤标志物呈阴性患者中有2例为肺癌[1例非小细胞肺癌(腺癌)、1例小细胞肺癌]、1例星形细胞瘤(腰髓)。(3)细胞学检查:23例患者均行脑脊液细胞学检查,显微镜下观察可见异形细胞,细胞体积增大,胞质深染呈强嗜碱性,胞核大而不规则、可见核仁;大量异形细胞聚集成团,部分细胞胞质有明显空泡(图1)。

四、影像学检查

本组23例患者中22例行头部MRI平扫和增强检查,均显示脑膜强化征象,其中13例(59.09%)脑膜强化伴脑室系统扩大;强化灶多见于双侧大脑半球软脑膜、脑沟、脑裂、颅底软脑膜、小脑幕等部位,呈弥漫性或线样强化,并可见双侧侧脑室扩大,前、后角圆钝,第三、第四脑室呈球形扩张(图2,3)。余1例仅行头部CT检查,显示幕上脑室系统扩大。

五、治疗及预后

1. 治疗原则 本组共12例患者完成为期2年随访,其中非小细胞肺癌(腺癌)脑膜转移8例、星形细胞瘤(腰髓)脑膜转移1例、B-NHL脑膜转移1例、胃癌(腺癌)脑膜转移1例,转移灶来源不详1例。其中7例[非小细胞肺癌(腺癌)6例、星形细胞瘤(腰髓)1例]确诊后接受药物化疗或放射治疗,5例放弃

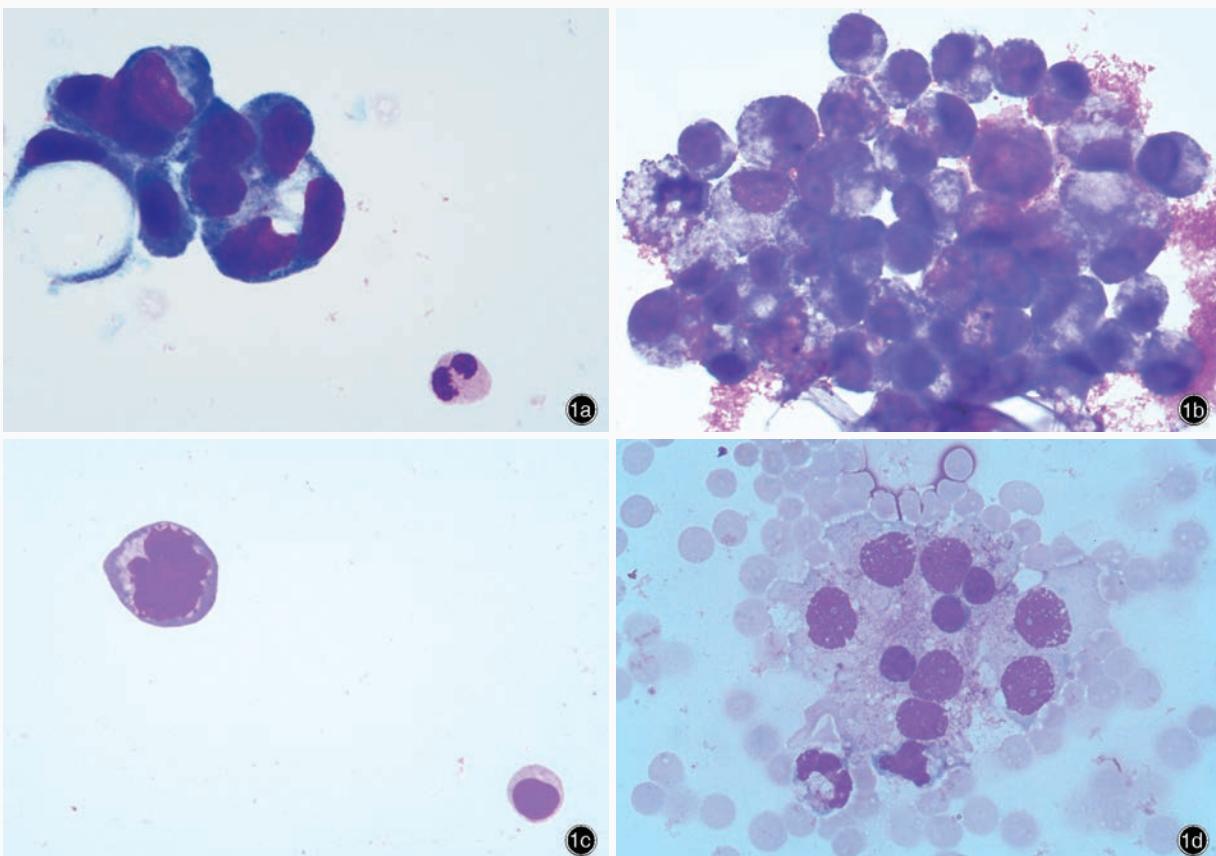


图1 光学显微镜观察 瑞姬染色 $\times 1000$ 1a 女性患者,52岁。以头痛、呕吐伴视力下降发病,临床诊断:非小细胞肺癌(腺癌)脑膜转移。镜下可见较多异形细胞,细胞聚集成团,胞体明显增大、核仁明显,胞质有明显空泡,部分细胞胞质呈强嗜碱性
1b 女性患者,40岁。以头痛、眩晕伴呕吐发病。临床诊断:结肠癌(腺癌)脑膜转移。镜下可见大量异形细胞,细胞聚集成团,胞体增大,胞质呈嗜碱性,可见核仁 1c 女性患者,67岁。以头痛、呕吐伴视力下降发病。临床诊断:淋巴瘤(B-NHL)脑膜转移。镜下可见异形细胞,胞体增大、胞核大而不规则,胞质呈深染、强嗜碱性 1d 女性患者,63岁。以抽搐、视力下降、行走不稳发病。临床诊断:星形细胞瘤(腰髓,WHO II级)脑膜转移。镜下可见明显异形细胞,胞体增大,胞核大、核仁明显,胞质呈嗜碱性

Figure 1 Optical microscopy findings Reggie staining $\times 1000$ A 52-year-old female patient was diagnosed as meningeal carcinomatosis from non-small cell lung cancer (adenocarcinoma) with headache, vomiting, and vision loss onset. Lots of atypical cells were observed and aggregated into clusters. The cells were enlarged, nucleolus obvious, cytoplasm vacuole and some were strongly basophilic (Panel 1a). A 40-year-old female patient was diagnosed as meningeal carcinomatosis from colon cancer (adenocarcinoma) with headache, vertigo and vomiting onset. A large number of atypical cells were observed and aggregated together under the microscope. The cells were enlarged, cytoplasm was basophilic and nucleus were visible (Panel 1b). A 67-year-old female patient was diagnosed as meningeal carcinomatosis from lymphoma (B-NHL) with headache, vomiting, and vision loss onset. Under microscopic observation, atypical cells were visible and the nucleus were large and irregular, the cytoplasm was deeply stained and strongly basophilic (Panel 1c). A 63-year-old female patient was diagnosed as meningeal carcinomatosis from spinal astrocytoma (WHO II) with epilepsy seizures, visual impairment, and instability onset. Under microscopic observation, atypical cells were seen and the cells were enlarged, nucleolus were obvious and cytoplasm was basophilic (Panel 1d).

治疗。(1)非小细胞肺癌(腺癌)脑膜转移:6例患者经基因检测显示,基因突变型(*EGFR*基因)1例、野生型5例。5例野生型患者中4例采取培美曲塞+顺铂方案化疗,同时联合奥沙替尼(AZD9291)靶向治疗,其中1例因疗效欠佳而改行全脑放射治疗(WBRT);余1例采用替莫唑胺化疗联合盐酸埃克替尼(凯美纳)靶向方案,亦因疗效欠佳而行全脑放疗。1例基因突变型患者单纯行AZD9291靶向治疗。(2)星形细胞瘤(腰髓)脑膜转移:行替莫唑胺化疗。上述7例患者,经药物化疗、靶向治疗或全脑

放射治疗后临床症状明显减轻、颅内压下降、脑膜强化灶减弱,提示治疗有效。

2. 随访与预后 本组7例接受治疗的患者中,有6例非小细胞肺癌(腺癌)脑膜转移患者至今生存,生存时间为4~17个月,平均为9.20个月,其中3例基本恢复正常生活,无头痛或其他不适;3例头痛症状减轻,但遗留视力及听力下降,日常生活可自理。1例星形细胞瘤(腰髓)脑膜转移患者,恢复正常生活,生存时间为24个月。5例放弃治疗病例均死亡,生存时间为2周至17个月,平均7.90个月。

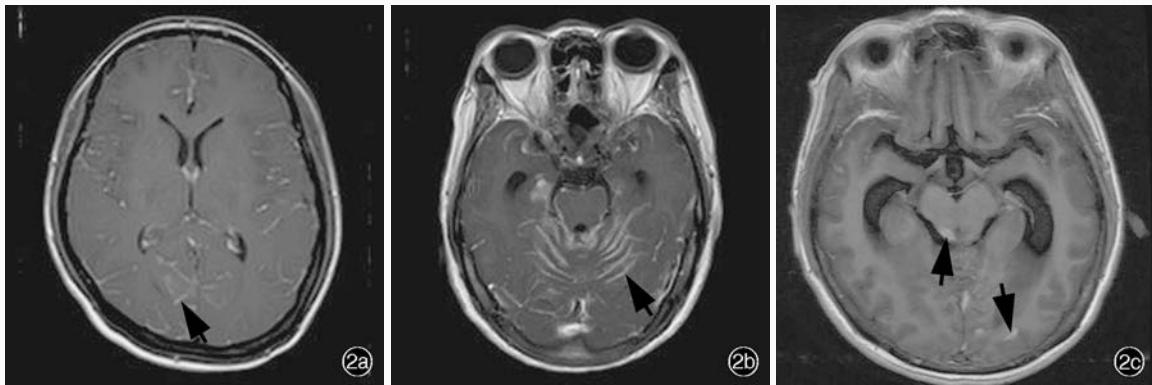


图2 头部MRI检查 2a 女性患者,61岁。临床诊断:非小细胞肺癌(腺癌)脑膜转移。横断面增强T₁WI可见双侧大脑半球脑沟内异常线样强化(箭头所示) 2b 男性患者,52岁。临床诊断:胃癌(腺癌)脑膜转移。横断面增强T₁WI显示双侧小脑半球、脑沟异常强化(箭头所示) 2c 女性患者,54岁。临床诊断:非小细胞肺癌(腺癌)脑膜转移。横断面增强T₁WI可见枕叶、脑沟、四叠体池弥漫性强化(箭头所示)

Figure 2 Head MRI findings A 61-year-old female patient was diagnosed as meningeal carcinomatosis from non-small cell lung cancer (adenocarcinoma). Axial enhanced T₁WI showed abnormal linear enhancement in the sulcus of bilateral cerebral hemisphere (arrow indicates, Panel 2a). A 52-year-old male patient was diagnosed as meningeal carcinomatosis from gastric cancer (adenocarcinoma). Axial enhanced T₁WI showed abnormal enhancement of bilateral cerebellar hemisphere and sulci (arrow indicates, Panel 2b). A 54-year-old female patient was diagnosed as meningeal carcinomatosis from non-small cell lung cancer (adenocarcinoma). Axial enhanced T₁WI showed diffuse enhancement of occipital lobe, sulci and quadrigeminal cistern (arrows indicate, Panel 2c).

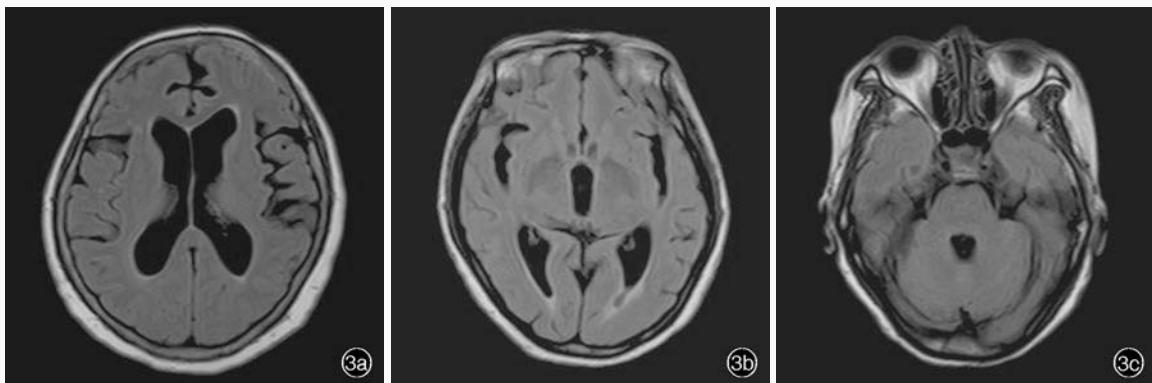


图3 头部MRI检查 3a 女性患者,54岁。临床诊断:星形细胞瘤(腰髓,WHO II级)脑膜转移。横断面FLAIR成像显示双侧侧脑室扩张,前、后角圆钝 3b 女性患者,58岁。临床诊断:非小细胞肺癌(腺癌)脑膜转移。横断面FLAIR成像显示第三脑室扩张 3c 女性患者,60岁。临床诊断:非小细胞肺癌(腺癌)脑膜转移。横断面FLAIR成像显示第四脑室呈轻度扩张

Figure 3 Head MRI findings A 54-year-old female patient was diagnosed as meningeal carcinomatosis from spinal astrocytoma (WHO II). Axial FLAIR showed expansion of bilateral lateral ventricles with blunt anterior and posterior horns (Panel 3a). A 58-year-old female patient was diagnosed as meningeal carcinomatosis from non-small cell lung cancer (adenocarcinoma). Axial FLAIR showed expansion of the third ventricle (Panel 3b). A 60-year-old female patient was diagnosed as meningeal carcinomatosis from non-small cell lung cancer (adenocarcinoma). Axial FLAIR showed mild expansion of the fourth ventricle (Panel 3c).

讨 论

脑膜癌是恶性肿瘤细胞通过脑脊液循环播散到软脑膜、脊膜、蛛网膜和蛛网膜下隙导致中枢神经系统功能障碍的一类疾病,临床以头痛、呕吐等颅内高压症状与体征为主要表现,尚具有多灶性脑神经和脊神经根受累的特点,但其临床表现缺乏特异性,在原发灶未被发现的情况下,丰富的临床经

验和脑脊液细胞学检查对疾病的诊断至关重要。

国内一项统计分析资料显示,94例脑膜癌患者的发病年龄为11~76岁,中位年龄55岁^[1];国外文献报道的中位发病年龄为56岁^[2]。本组病例发病年龄最大者为75岁、最小31岁,但以40~70岁年龄段较为高发,中位年龄54岁,与以上文献报道相符。其中男性7例,女性16例,男女比例约为1:2.29,以女性病例多见。

脑膜癌患者通常肿瘤细胞沿软脑膜呈弥漫性浸润,累及大脑半球、脑神经、软脑膜,临床以头痛、呕吐、视力下降等颅内高压症状为主,同时可伴有复视、视力下降、面部麻木、听力下降、眩晕等其他脑神经受累症状与体征,脊神经根受累时则可出现颈背部疼痛,双下肢无力、麻痹等,亦可见脑病样表现或癫痫发作等^[3]。本组23例中20例(86.96%)表现为明显或剧烈的头痛症状,12例(52.17%)伴反复呕吐、10例(43.48%)伴明显视力下降,符合颅内高压为脑膜癌的典型临床表现的特点。值得注意的是,所有患者病程中均无发热症状,因此临幊上对于颅内高压而不伴发幊的病例应高度警惕脑膜癌的可能。

据资料统计,95.76%的脑膜癌源于实体肿瘤转移、3.66%来源于血液系统肿瘤,仅有0.58%来源不明,在所有实体肿瘤中,原发肿瘤为肺癌者最为常见,占所有登记病例的64.35%^[2],其中以非小细胞肺癌多见^[4];其次分别为乳腺癌18.50%^[2,5]、胃肠道肿瘤7.51%(如胃癌^[6]、食管癌^[7]、胰腺癌^[8]、直肠癌^[9]、结肠癌^[10]);也可源于膀胱癌^[11]、卵巢癌^[12]、前列腺癌^[13];而鼻窦癌^[14]或鼻咽癌^[15]则极为少见。本组23例中15例(65.22%)原发灶为肺癌、1例(4.35%)结肠癌、1例(4.35%)B-NHL、1例(4.35%)胃癌、1例(4.35%)星形细胞瘤(腰髓)、4例(17.39%)来源不详,与上述文献报道数据基本相符,但来源不详者比例偏高,可能与部分患者未进行全面肿瘤筛查有关。

影像学检查对脑膜癌虽无特异性,但具有十分重要的提示意义。据国外研究显示,仅有35%的患者可通过MRI明确诊断、22%由脑脊液细胞学诊断,而42%的患者需要通过上述两种方法共同提供证据方能确诊^[2]。脑膜癌最突出的影像学特征为MRI增强扫描可见脑膜异常强化,并伴有明显的交通性脑积水^[3,16]。本组22例接受头部MRI检查的患者,软脑膜均呈明显强化征象,其中13例(59.09%)软脑膜强化伴脑室系统扩大;1例行头部CT检查者呈脑室系统扩大。因此,MRI增强扫描对于头痛患者的诊断十分重要,尤其是表现为明显头痛但临床症状又不符合原发性头痛症状特点的患者,及时的头部MRI增强扫描可为临床诊断提供极为重要的参考信息。对于呈明显脑膜强化征象者,则需考虑脑膜炎症或脑膜癌的可能,伴交通性脑积水者,腰椎穿刺脑脊液检查是必不可少的。

脑脊液细胞学筛查肿瘤细胞是脑膜癌诊断的“金标准”,脑脊液压力明显升高也是脑膜癌的重要临幊特点之一^[17]。本组有19例(82.61%)患者颅内压明显升高,11例(47.83%)>330 mm H₂O;16例(69.57%)白细胞计数轻度升高,19例(82.61%)蛋白定量明显升高、6例(26.09%)葡萄糖水平下降。可见脑脊液常规、生化检查对脑膜癌的诊断无特异性,但脑脊液压力明显升高伴白细胞计数轻度升高、葡萄糖水平下降,以及蛋白定量水平升高对脑膜癌的诊断亦有一定的提示意义。此外,许多研究业已表明,血液和脑脊液肿瘤标志物筛查对诊断具有重要参考意义。Shi等^[18]的临幊资料显示,脑膜癌患者脑脊液肿瘤标志物CEA、CA125、CA199、细胞角蛋白21-1(CYFRA21-1)和血清肿瘤标志物CEA、CA125、CA153、CA199和甲胎蛋白(AFP)均高于正常对照者,特别是CEA、CA125、CA199和CYFRA21-1水平升高有助于早期诊断。我们对本组17例患者进行了血清肿瘤标志物筛查,11例CEA水平升高,其中9/11例为非小细胞肺癌(腺癌)、6例肿瘤标志物呈阴性;10例行脑脊液肿瘤标志物筛查,7例CEA水平升高,6/7例为非小细胞肺癌(腺癌),其余3例肿瘤标志物阴性。由此可见,脑膜癌患者血液和脑脊液肿瘤标志物,尤其是CEA水平可明显升高,与上述文献报道相符。虽然脑脊液肿瘤标志物水平升高可为脑膜癌的诊断提供重要参考信息,但结果呈阴性者亦不能排除诊断。因此,我们认为,对于来源于肺、胃肠道等部位的脑膜转移癌,肿瘤标志物筛查的阳性率较高,而对于来源于血液系统、神经系统的脑膜转移癌,其血液和脑脊液肿瘤标志物筛查的阳性率则较低。

脑膜癌是肿瘤的晚期阶段,患者预后不良。既往文献报道的平均生存期仅约3个月^[2],国内研究认为,接受药物化疗的患者平均生存期约为150天,而未行药物化疗患者的中位生存期仅为28天^[1]。也有学者报道,脑膜癌患者若早期行鞘内药物化疗其预后可明显改善,中位生存期可达5.20个月,其3、6和12个月的生存率分别为71.6%、49.2%和30.7%^[19]。根据对本组病例的观察,我们认为脑膜癌患者的生存期已明显延长,本组7例接受药物化疗、靶向治疗或全脑放射治疗的患者目前均生存,平均生存期逾9.20个月,5例放弃治疗者均死亡,平均生存期7.90个月,提示积极接受治疗的患者生存期较既往文献报道有所延长。本研究结果表明,随

着医疗水平的不断提高,对脑膜癌患者的早诊早治成为可能;同时随着肿瘤治疗手段的进步尤其是靶向治疗药物的应用,大大提高了恶性肿瘤的治疗效果,使患者生存期明显延长。

利益冲突 无

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· 小词典 ·

中英文对照名词词汇(四)

- 脑白质高信号 white matter hyperintensity(WMH)
- 脑淀粉样血管病 cerebral amyloid angiopathy(CAA)
- 脑默认网络 default mode network(DMN)
- 脑微出血 cerebral microbleeds(CMBs)
- 脑小血管病 cerebral small vessel disease(cSVD)
- 脑血流量 cerebral blood flow(CBF)
- 脑卒中后抑郁 post-stroke depression(PSD)
- 颞叶内侧癫痫 medial temporal lobe epilepsy(mTLE)
- 帕金森病 Parkinson's disease(PD)
- 皮质发育畸形 malformation of cortical development(MCD)

- ¹¹C-匹兹堡复合物 B ¹¹C-Pittsburgh compound B(¹¹C-PIB)
- 腔隙性梗死 lacunar infarct(LACI)
- 全面性周期性放电 generalized periodic discharges(GPDs)
- 全脑放射治疗 whole brain radiation therapy(WBRT)
- 人类免疫缺陷病毒 human immunodeficiency virus(HIV)
- 日常生活活动能力量表 Activities of Daily Living(ADL)
- 神经梅毒 neurosyphilis(NS)
- 神经炎性斑 neuritic plaques(NPs)
- 神经原纤维缠结 neurofibrillary tangles(NFTs)