·临床病理报告·

(颈椎)上皮样恶性外周神经鞘瘤:一例报告并文献复习

陈娟芝 曾迎玥 黎相照 薛小磊 韩慧霞

【摘要】 **研究背景** 上皮样恶性外周神经鞘瘤为临床少见的软组织恶性肿瘤,以成年男性多见。肿瘤起源于大神经,主要发生于四肢、头颈部和脊柱,为侵袭性肿瘤,局部复发率高,约有50%的患者可出现远隔部位转移。本文旨在探讨(颈椎)上皮样恶性外周神经鞘瘤的临床病理学特征。**方法与结果** 男性患者,48岁。临床主要表现为肢体无力,以左下肢明显,并伴足踝部肿胀。MRI检查显示C_{3-5}椎管内占位性病变,考虑椎管内肿瘤术后复发。经枕外隆突至C_7水平行颈椎椎管内肿瘤切除、硬脊膜修补及椎板减压术。术中可见肿瘤大部位于C_{3-5}水平脊神经前方、左侧椎管内和硬脊膜外,由于部分肿瘤已经固定的钛板开口向前方生长,无法全切除。术后组织形态学观察,肿瘤细胞呈片状或巢团状排列,可见神经纤维分隔,大部分肿瘤细胞呈上皮样、少部分呈梭形,核分裂象易见,部分区域可见灶性坏死。肿瘤细胞弥漫表达波形蛋白、广谱细胞角蛋白、上皮膜抗原、S-100蛋白、突触素和嗜铬素A;不表达肌动蛋白、结蛋白、黑色素瘤相关抗原HMB45、胶质纤维酸性蛋白、孕激素受体、CD34和CD31;Ki-67抗原标记指数>25%;网状纤维染色可见网状纤维包绕上皮样细胞巢;荧光原位杂交检测*SS18*基因易位阴性。结合病史,最终诊断为(颈椎)上皮样恶性外周神经鞘瘤。**结论** 上皮样恶性外周神经鞘瘤组织形态学表现缺乏特征性,易与其他软组织上皮样肿瘤相混淆,须结合患者临床表现、组织形态学和临床免疫表型综合判断,以免引起误诊或漏诊。S-100蛋白检测虽缺乏特异性,但仍不失为一项诊断上皮样恶性外周神经鞘瘤有价值的指标,广谱细胞角蛋白和上皮膜抗原可呈强阳性表达。

【关键词】 神经鞘瘤; 软组织肿瘤; 颈椎; 免疫组织化学; 病理学

Epithelioid malignant peripheral nerve sheath tumor: a case report and review of literature

CHEN Juan-zhi, ZENG Ying-yue, LI Xiang-zhao, XUE Xiao-lei, HAN Hui-xia

Department of Pathology, School of Basic Medical Sciences, Department of Pathology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, Guangdong, China

Corresponding author: HAN Hui-xia (Email: hhxia@fimmu.com)

【Abstract】 **Background** Epithelioid malignant peripheral nerve sheath tumor (EMPNST) is a rare malignant soft tissue tumor, and is more common in adult male. EMPNST originates from nerve, mainly located in the limbs, head and neck, and spine. It is an aggressive tumor with high tendency for local recurrence, and about half of the cases appear distant metastasis. This paper aims to investigate the clinicopathological features of cervial EMPNST. **Methods and Results** A 48-year-old male mainly presented weakness of limbs, expecially left lower extremty with ankle swelling. MRI showed space-occupying lesion in segment C_{3-5}, considering recurrence of intraspinal tumor 2 years after operation. Tumor resection, repairing of spinal dura mater and laminectomy were made from inion to C_7 level. It was found during the surgery that most part of the tumor was located in front of C_{3-5} spinal nerve, left intraspinal and outside of dura mater. Because part of the tumor grew through the opening of titanium plate, the tumor could not be totally removed. According to postoperative histomorphological observation, tumor cells arranged in sheets or nests, and were separated by fibrous tissue. Most tumor cells were epithelioid, while small part of tumor cells were fusiform. Frequent mitotic activity was found, and part of the region appeared focal necrosis. Immunohistochemical staining showed that tumor cells were positive for pan

doi:10.3969/j.issn.1672-6731.2013.11.008

基金项目:国家自然科学基金青年科学基金资助项目(项目编号:81201960);广东省自然科学基金资助项目(项目编号:S2011040003730)

作者单位:510515 广州,南方医科大学基础医学院病理学系,南方医科大学附属南方医院病理科

通讯作者:韩慧霞(Email:hhxia@fimmu.com)

cytokeratin (PCK), epithelial membrane antigen (EMA), vimentin (Vim), synaptophysin (Syn), chromogranin A (CgA), and S-100 protein (S-100); and were negative for actin, desmin (Des), progestrone receptor (PR), glial fibrillary acidic protein (GFAP), CD34, CD31 and HMB45; Ki-67 labeling index was above 25%. Reticular fiber staining showed that the epithelioid cell nests were surrounded by reticular fibers. Fluorescence in situ hybridization (FISH) detection showed negative for *SS18* gene translocation. Combining with the history, the final pathological diagnosis was cervical EMPNST. **Conclusion** EMPNST lacks of morphological characteristics, and needs to be differentiated from a variety of benign or malignant tumors exhibiting epithelioid features. It is considered that clinical materials, morphological features and immunophenotype are helpful to avoid confusion with other similar lesions. S-100 is not a specific marker, but is a valuable diagnostic index. PCK and EMA can present strongly positive expression.

【Key words】 Neurilemmoma; Soft tissue neoplasms; Cervical vertebrae; Immunohistochemistry; Pathology

This study was supported by National Natural Science Foundation of China (No. 81201960) and Natural Science Foundation of Guangdong Province (No. S2011040003730).

恶性外周神经鞘瘤(MPNST)又称神经肉瘤、神经纤维肉瘤或恶性神经鞘瘤,占所有软组织肉瘤的5%~10%,肿瘤细胞起源于许旺细胞[1-2],呈上皮样分化的恶性外周神经鞘瘤临床鲜见[3]。南方医科大学附属南方医院病理科近年明确诊断1例(颈椎)上皮样恶性外周神经鞘瘤(EMPNST)患者,笔者拟结合文献,探讨其临床病理学特征及诊断要点。

病历摘要

患者 男性,48岁。主诉$C_{3\sim5}$椎管内肿瘤切除术后2年、肢体无力1月余,于2012年11月12日入院。患者2年前因颈椎肿瘤于外院施行肿瘤切除术,术后病理报告:椎管内恶性肿瘤(滑膜肉瘤、脊膜瘤?)。未行放射治疗和药物化疗,恢复尚可。入院前1月余突发肢体无力,以左侧明显,尤其左下肢完全不能活动伴足踝部肿胀。无头痛、头晕,无恶心、呕吐,无抽搐。外院MRI检查显示,颈椎椎管内肿瘤复发。为求进一步明确诊断并接受治疗至我院就诊。

既往史及家族史 患者2年前于外院行颈椎椎管内肿瘤切除术。无疫区、疫情、疫水接触史,无吸烟、饮酒史。否认家族遗传史、家族性肿瘤史。

入院后体格检查 体温36 ℃,呼吸18次/min,脉搏80次/min,血压120/80 mm Hg(1 mm Hg = 0.133 kPa)。发育正常,表情自如,神志清楚,言语流利。神经系统专科检查:左上肢肌力3级、左下肢0级,肌肉严重萎缩、生理反射消失、病理反射未引出;右侧肢体肌力4级,生理反射存在、病理反射未引出。其余无可述及。

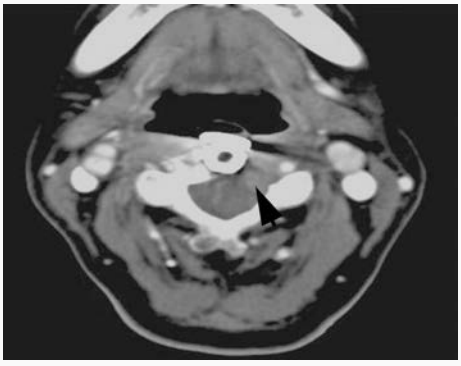

图1 横断面增强CT扫描显示,左侧C_5椎体骨质缺如,可见一团块状强化影,向椎管内突入,边界尚可分辨(箭头所示)

Figure 1 Axial enhanced CT showed deficiency of left C_5 vertebra and an enhanced mass which penetrated into the spinal canal with distinguished boundary (arrow indicates).

诊断与治疗经过 入院后CT检查显示,$C_{3\sim5}$椎体左侧骨质缺如,增强扫描可见一团块状强化影,并突入椎管内生长,边界尚可分辨,约为2.60 cm × 1.20 cm大小,双侧颈动脉鞘区未见明显肿大的淋巴结影(图1)。临床诊断:$C_{3\sim5}$椎管内肿瘤术后,相应层面椎管内占位性病变,考虑肿瘤复发。于2012年11月20日在全身麻醉下经枕外隆突至C_7水平纵行直切口施行颈椎椎管内肿瘤切除、硬脊膜修补及椎板减压术。术中可见肿瘤大部分位于$C_{3\sim5}$水平脊神经前方、左侧椎管内和硬脊膜外,沿肿瘤边界切除直至椎体前方固定的钛板,部分肿瘤已经钛板开口向前方生长,无法完全切除。术后予以对症支持治疗,由于患者一般情况较差、呼吸肌无力,家属放弃治疗,于2012年12月2日出院。(1)大体标本观察:

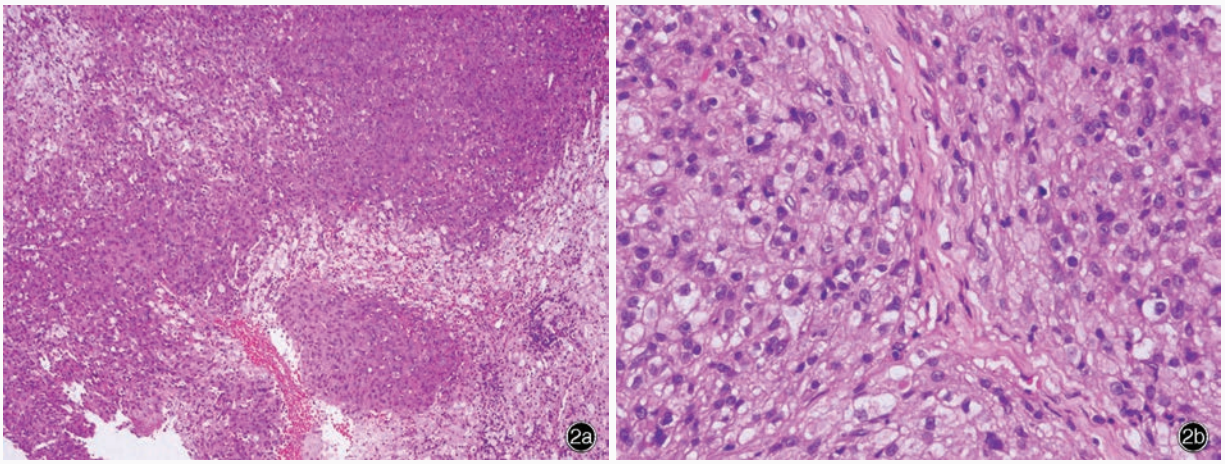

图2 光学显微镜观察所见 HE染色 2a 肿瘤细胞呈巢团状排列，细胞密集区与稀疏区交叉排列 ×40 2b 肿瘤细胞呈上皮样，可见胞质空泡化 ×200

Figure 2 Optical microscopy findings. HE staining The tumor cells arranged in nests. Dense areas and sprase areas were crosswise arranged (Panel 2a). ×40 The tumor cells were epithelioid, and cytoplasmic vacuolation could be found (Panel 2b). ×200

手术切除的肿瘤组织标本为灰白、灰褐色破碎组织块，大小约为3.00 cm×2.00 cm×0.70 cm，剖面呈黄白色，血运一般，质地较脆。(2)组织形态学观察：经体积分数为4%中性甲醛溶液固定，常规制片，行HE染色。光学显微镜下观察肿瘤呈多结节状或巢团状，细胞密集区与稀疏区交叉排列(图2a)，梭形肿瘤细胞包绕或穿行于上皮样肿瘤细胞巢之间，大部分肿瘤细胞呈上皮样，为圆形或多边形，排列密集，细胞核较大、多为圆形，核仁明显，细胞质丰富、嗜酸性，部分肿瘤细胞胞质呈空泡化(图2b)；上皮样肿瘤细胞周围可见另一种梭形肿瘤细胞成分，细胞肥胖，似纤维母细胞，细胞质依然较丰富、嗜酸性，呈不典型“栅栏”状排列，两种肿瘤细胞移行过度，核分裂象易见(5个/10个高倍视野)，细胞异型性明显，尚可见小灶性坏死；局部区域可见肿瘤细胞与神经纤维关系密切。(3)网状纤维染色：高锰酸钾氧化、草酸漂白、硫酸铁胺媒染，再滴加氨银溶液染色，体积分数为20%中性甲醛溶液还原，氯化金溶液调色，硫代硫酸钠溶液处理后常规无水乙醇脱水、二甲苯透明，光学显微镜观察。可见网状纤维与肿瘤细胞关系密切，肿瘤细胞巢与肿瘤细胞之间有大量纤细、疏松排列的网状纤维，分布较均匀，但并不包绕每个肿瘤细胞。(4)免疫组织化学染色：标记用Ⅰ抗，如波形蛋白(Vim)、S-100蛋白(S-100)、广谱细胞角蛋白(PCK)、上皮膜抗原(EMA)、Ki-67抗原、胶质纤维酸性蛋白(GFAP)、肌动蛋白(actin)、结蛋白(Des)、黑色素瘤相关抗原HMB45、嗜铬素A(CgA)和突触素(Syn)等，均购自北京中杉金桥生物技术有限公司，EnVision™试剂盒购自丹麦Dako公司。采用EnVision二步法高温、高压修复抗原，二氨基联苯胺(DAB)显色，光学显微镜观察。肿瘤细胞弥漫表达波形蛋白(图3a)、广谱细胞角蛋白(图3b)、上皮膜抗原(图3c)、S-100蛋白(图3d)和突触素，灶性表达嗜铬素A，Ki-67抗原标记指数>25%；不表达肌动蛋白、结蛋白、HMB45、胶质纤维酸性蛋白、孕激素受体(PR)、CD34和CD31。(5)荧光原位杂交(FISH)检测：PathVysion SSX18探针试剂盒购自基因科技(上海)有限公司，采用双色断裂分离探针检测*SS18*基因易位情况。4′,6-二脒基-2-苯基吲哚(DAPI)复染后，日本Olympus BX-51荧光显微镜观察，Video Test FISH 2.0软件合成图像。结果显示，*SS18*基因易位呈阴性。

讨 论

上皮样恶性外周神经鞘瘤细胞异型性明显、组织结构复杂，临床诊断有一定困难。但根据上皮样肿瘤细胞呈片状、巢团状或结节状分布，以及梭形肿瘤细胞移行过度等组织学特点，结合免疫组织化学染色波形蛋白和特异性免疫学标志物S-100蛋白表达阳性可明确诊断。该例患者在诊断过程中，免疫组织化学染色上皮组织来源肿瘤标志物(广谱细胞角蛋白、上皮膜抗原)和间叶组织来源肿瘤标志物(波形蛋白)均呈弥漫高表达，经检索相关文献未见类似报道。波形蛋白在部分低分化癌、几乎全部

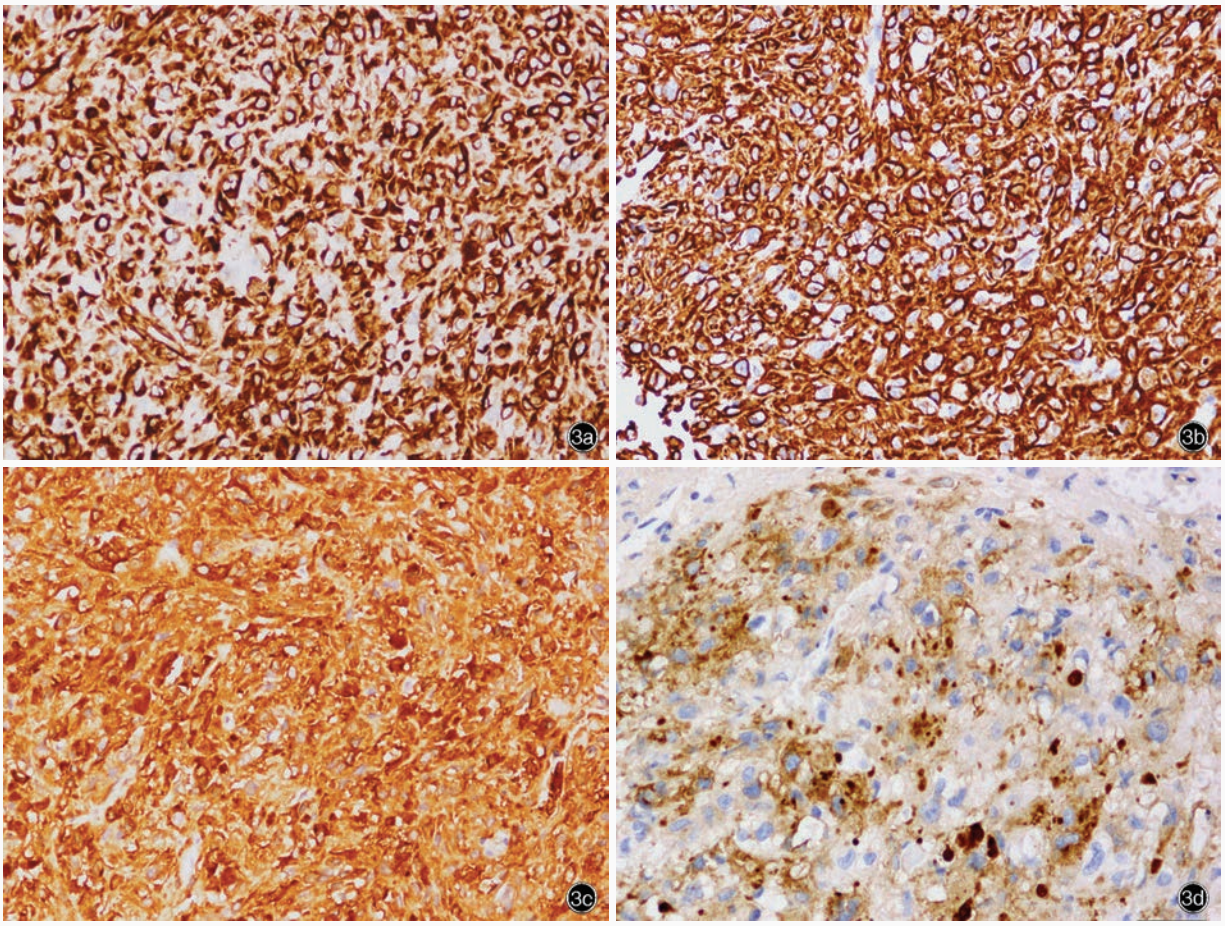

图3 光学显微镜观察所见 免疫组织化学染色(EnVision二步法) ×200 3a 肿瘤细胞胞膜弥漫高表达波形蛋白 3b 肿瘤细胞胞膜弥漫高表达广谱细胞角蛋白 3c 肿瘤细胞胞膜弥漫高表达上皮膜抗原 3d 肿瘤细胞胞质弥漫高表达S-100蛋白

Figure 3 Optical microscopy findings. Immunohistochemical staining (EnVision) ×200. Vim presented diffusely strong positivity in tumor cell membrane (Panel 3a). PCK presented diffusely strong positivity in tumor cell membrane (Panel 3b). EMA presented diffusely strong positivity in tumor cell membrane (Panel 3c). S-100 presented diffusely strong positivity in tumor cell cytoplasm (Panel 3d).

软组织肿瘤中均呈高表达,对鉴别诊断无意义。一般认为,上皮样恶性外周神经鞘瘤不表达上皮组织来源肿瘤标志物(广谱细胞角蛋白、上皮膜抗原)。有文献报道,上皮样恶性外周神经鞘瘤上皮组织来源肿瘤标志物(广谱细胞角蛋白、上皮膜抗原)表达阴性[4-10];黄斌等[11]报告7例病例,仅3例上皮样肿瘤细胞巢区域弱阳性表达上皮膜抗原,均不表达广谱细胞角蛋白;赵红艳等[12]和祝斌等[13]报告的病例仅部分表达上皮膜抗原,而不表达广谱细胞角蛋白。有研究显示,双相型滑膜肉瘤上皮和间叶组织均表达广谱细胞角蛋白和上皮膜抗原[14],其组织学形态与上皮样恶性外周神经鞘瘤有重叠,且免疫组织化学检测肿瘤细胞亦表达S-100蛋白,为此我们进行了荧光原位杂交检测,结果显示*SS18*基因易位阴性,从而排除了滑膜肉瘤的诊断。该例患者光学显微镜下可见肿瘤细胞与周围神经纤维关系密切,网状纤维染色显示肿瘤细胞巢与肿瘤细胞之间均有网状纤维包绕,结合其他免疫表型,最终诊断为(颈椎)上皮样恶性外周神经鞘瘤。

由于上皮样恶性外周神经鞘瘤临床特征及肿瘤细胞组织形态学变化缺乏特异性,临床诊断存在很大困难,因此免疫组织化学染色等检测方法对明确诊断与鉴别诊断是不可或缺的。特异性肿瘤标志物S-100蛋白表达阳性有助于明确诊断,而其他肿瘤标志物的表达尚存在不确定性,如广谱细胞角蛋白和上皮膜抗原也可呈高表达。

参 考 文 献

[1] Enzinger FM, Weiss SW. Soft tissue tumors. 4th ed. St. Louis: Mosby, 2001: 1167-1170.

[2] Liu XY, Zhang S, Wang XF, Chen YP. Clinicopathological

features of lymph node metastatic EMPNST: a case report and review of literatures. Zhongguo Xian Dai Shen Jing Ji Bing Za Zhi, 2012, 12:175-183.[刘雪咏, 张声, 王行富, 陈余朋. 上皮样恶性外周神经鞘膜瘤淋巴结转移临床病理学特征:病例报告及文献复习. 中国现代神经疾病杂志, 2012, 12:175-183.]

[3] Dodd LG, Scully S, Layfield LJ. Fine-needle aspiration of epithelioid malignant peripheral nerve sheath tumor (epithelioid malignant schwannoma). Diagn Cytopathol, 1997, 17:200-204.

[4] Agaimy A, Stachel KD, Jüngert J, Radkow T, Carbon R, Metzler M, Holter W. Malignant epithelioid peripheral verve sheath tumor with prominent reticular/microcystic pattern in a child: a low-grade neoplasm with 18-years follow-up. Appl Immunohistochem Mol Morphol, 2011.[Epub ahead of print]

[5] Gulati N, Rekhi B, Suryavanshi P, Jambhekar NA. Epithelioid malignant peripheral nerve sheath tumor of the uterine corpus. Ann Diagn Pathol, 2011, 15:441-445.

[6] Gao FP, Wei J, Xia LH, Qin DM, Sun Q. Epitheloid malignant peripheral nerve sheath tumor: a case report and review of literatures. Xian Dai Zhong Liu Yi Xue, 2013, 21:186-187.[高福平, 魏谨, 夏莉花, 秦冬梅, 孙琼. 颈椎上皮样恶性外周神经鞘膜瘤的诊断. 现代肿瘤医学, 2013, 21:186-187.]

[7] Cao JL, Ma XB, Wang ZF, Yu WC, Chen HL. A case report of malignant peripheral nerve sheath tumor in nasal cavity. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi, 2010, 24:89-90.[曹金玲, 马小兵, 王张锋, 于文成, 陈红林. 鼻腔恶性外周神经鞘膜瘤1例. 临床耳鼻咽喉头颈外科杂志, 2010, 24:89-90.]

[8] Zeng W, Zheng YQ, Zhang ZG, Chen SJ. A case report of malignant peripheral nerve sheath tumor in auricle. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi, 2009, 23:424-425.[曾薇, 郑亿庆, 张志钢, 陈穗俊. 耳廓恶性外周神经鞘膜瘤1例. 临床耳鼻咽喉头颈外科杂志, 2009, 23:424-425.]

[9] Zhao GL, Sha C, Cui Z, Li ZH. A case report of malignant peripheral nerve sheath tumor with frontal bone metastasis. Zhongguo Lin Chuang Shen Jing Wai Ke Za Zhi, 2010, 15:382.[赵国良, 沙成, 崔壮, 李增华. 恶性外周神经鞘膜瘤额骨转移1例. 中国临床神经外科杂志, 2010, 15:382.]

[10] Li CG, Yang LY. A case report of malignant peripheral epitheloid nerve sheath tumor. Shi Yong Yi Xue Za Zhi, 2007, 23:1476.[李春光, 杨丽媛. 上皮样恶性外周神经鞘膜瘤1例. 实用医学杂志, 2007, 23:1476.]

[11] Huang B, Zhai MJ, Cai LB, Sun LJ. Clinicopathologic analysis of seven cases of malignant peripheral nerve sheath tumor. Shi Yong Zhong Liu Xue Za Zhi, 2007, 21:360-361.[黄斌, 翟梅娟, 蔡路兵, 孙丽君. 恶性外周神经鞘膜瘤7例临床病理分析. 实用肿瘤学杂志, 2007, 21:360-361.]

[12] Zhao HY, Zhang ZG, Tang JL. A case report of malignant peripheral epitheloid nerve sheath tumor in the right knee. Di San Jun Yi Da Xue Xue Bao, 2004, 26:2214.[赵红艳, 张哉根, 汤金梁. 右膝部上皮样恶性外周神经鞘瘤1例. 第三军医大学学报, 2004, 26:2214.]

[13] Zhu B, Liu XG, Liu ZJ, Jiang L, Wei F, Ma QJ, Dang GD. Management of primary spinal intraosseous malignant peripheral nerve sheath tumor. Zhongguo Ji Zhu Ji Sui Za Zhi, 2010, 20:385-389.[祝斌, 刘晓光, 刘忠军, 姜亮, 韦峰, 马庆军, 党耕町. 脊柱原发恶性外周神经鞘膜瘤的诊断与治疗. 中国脊柱脊髓杂志, 2010, 20:385-389.]

[14] Wang F, Shao Q, Zhang X, Wu QL, Kuang YL, Shao JY. Diagnostic value of dual-color break-apart in situ hybridization for detection of SS18 rearrangement in synovial sarcoma. Zhongshan Da Xue Xue Bao (Yi Xue Ke Xue Ban), 2012, 33:251-254.[王芳, 邵琼, 张旭, 吴秋良, 匡亚玲, 邵建永. 荧光原位杂交技术检测滑膜肉瘤SS18基因易位的诊断价值. 中山大学学报(医学科学版), 2012, 33:251-254.]

(收稿日期:2013-09-12)

·小词典·

中英文对照名词词汇(二)

髓周动-静脉瘘 perimedullary arteriovenous fistula(PMAVF)

胎牛血清 fetal bovine serum(FBS)

糖类抗原 carbohydrate antigen(CA)

体感诱发电位 somatosensory-evoked potentials(SEPs)

体质量指数 body mass index(BMI)

微管相关蛋白 microtubule-associated protein(MAP)

无进展生存期 progression free survival(PFS)

选择性5-羟色胺再摄取抑制药 selective serotonin reuptake inhibitor(SSRI)

荧光原位杂交 fluorescence in situ hybridization(FISH)

硬脊膜动-静脉瘘 spinal dural arteriovenous fistula(SDAVF)

有限元分析 finite element analysis(FEA)

有限元模型 finite element model(FEM)

运动诱发电位 motor-evoked potentials(MEPs)

载脂蛋白A apolipoprotein A(ApoA)

中国精神障碍分类与诊断标准第3版 Classification and Diagnostic Criteria of Mental Disorders in China-Third-Edition(CCMD-3)

椎旁动-静脉瘘 paravertebral arteriovenous fistula(PVAVF)

自旋回波序列 spin echo sequence(SE)

Churg-Strauss综合征 Churg-Strauss syndrome(CSS)

Rett综合征 Rett syndrome(RS)

总睡眠时间 total sleep time(TST)