·病例报告·

脑桥小脑角听神经瘤和脑膜瘤的碰撞瘤一例

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【关键词】 神经纤维瘤病2型； 神经瘤,听； 脑膜瘤； 病例报告
【Key words】 Neurofibromatosis 2; Neuroma, acoustic; Meningioma; Case reports

A collision of vestibular schwannoma and meningioma in the cerebellopontine angle: one case report

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患者 女性,30岁。因颅内及椎管内多发神经纤维瘤切除术后17年,左耳耳鸣伴听力下降2个月,于2018年9月6日入院。患者17年前无明显诱因出现右下肢无力,当地医院全脊椎MRI检查(2001年5月23日)显示椎管内髓外硬膜下多发占位,考虑患者无力症状因C_5椎管内较大体积占位性病变压迫所致,予以手术切除,术后病理提示神经纤维瘤;术后为进一步筛查行头部MRI检查,显示颅内幕上及幕下多发占位,双侧脑桥小脑角区占位,考虑"Ⅱ型神经纤维瘤病(NF2)",由于左侧脑桥小脑角区占位性病变体积较大,于2001年12月3日在当地医院行局部立体定向放射治疗(具体方案及剂量不详);此后每年复查一次,发现颅内及椎管内多发占位进行性增多、增大,于2016年12月16日及2017年5月17日在当地医院分别行$L_{3\sim4}$椎管内占位性病变切除术及左侧小脑占位性病变切除术,术后病理分别提示为神经鞘瘤和纤维型脑膜瘤;2个月前无明显诱因突发左耳"蝉鸣"样耳鸣,间歇发作,伴左耳听力减退,左侧面部麻木,行走不稳,向左侧偏斜。患病期间无恶心、呕吐,无肢体无力、视物不清、意识障碍等症状。为求进一步诊断与治疗,于2018年9月4日至我院就诊,门诊以"颅内多发占位性病变"收入院。患者自发病以来,精神、饮食、睡眠尚可。既往史、个人史及家族史均无特殊。

入院后诊断与治疗经过 体格检查:体温36.4 ℃,心率78次/min,呼吸15次/min,血压为112/68 mm Hg(1 mm Hg = 0.133 kPa),心、肺、腹部检查无明显异常。神志清楚,语言流利;双侧瞳孔等大、等圆,直径约为2.50 mm,对光反射灵敏,各向眼动充分,无眼震;双耳听力粗测减退,以左侧为著;左侧面部浅感觉减退,左侧House-Brackmann(H-B)分级Ⅱ级,伸舌居中;四肢肌力、肌张力、腱反射正常;左侧指鼻试验、跟-膝-胫试验欠稳准,Romberg征阳性,Babinski征阴性,脑膜刺激征阴性。纯音测听检查显示左耳感音神经性听力减退,言语识别率(SDS)显著降低。脑干听觉诱发电位(BAEP)显示左侧Ⅴ波波幅降低,潜伏期延长,提示蜗后病变。实验室检查无明显异常。影像学检查:头部MRI显示双侧听神经不规则膨大,左侧脑桥小脑角区类圆形等T_1、稍长T_2信号影,边界清晰,大小约3.10 cm × 3.70 cm × 3.20 cm,邻近脑干及小脑受压向内侧移位,增强后可见病灶显著均匀强化(图1),考虑"双侧听神经瘤"。综合临床症状、病史及辅助检查诊断为Ⅱ型神经纤维瘤病,于2018年9月18日在全身麻醉下经左侧枕下乙状窦后入路行脑桥小脑角肿瘤切除术,显微镜下可见病灶质地柔软,呈灰红色,血供较丰富,广基底附着于岩骨背侧硬膜,并延续至小脑幕,断基底及血供后分块切除外侧肿瘤;深

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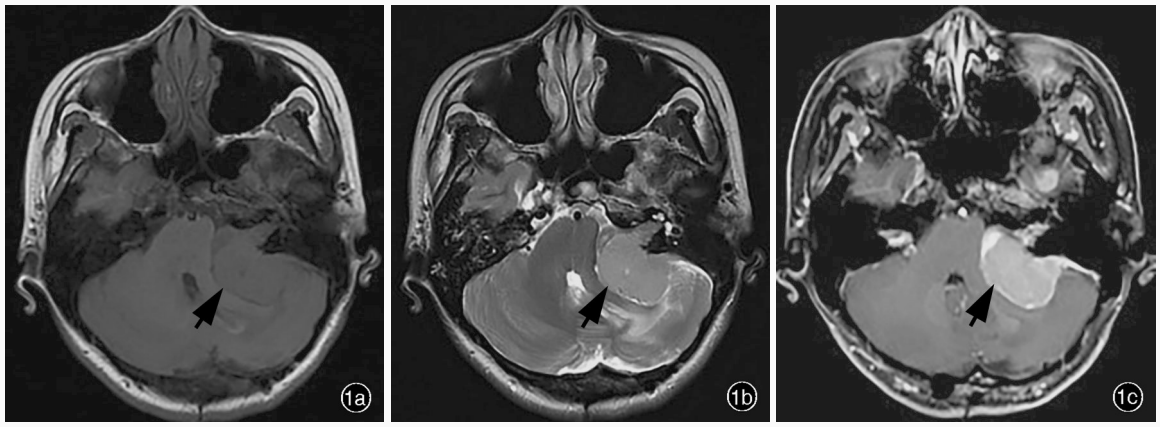

图1 术前头部MRI检查所见 1a 横断面T_1WI显示左侧脑桥小脑角及双侧内听道占位性病变呈等信号影(箭头所示),邻近左侧桥臂、脑干受压 1b 横断面T_2WI显示左侧脑桥小脑角及双侧内听道占位性病变呈稍高信号影(箭头所示),左侧病变压迫同侧桥臂及小脑,可见左侧小脑水肿 1c 横断面抑脂增强T_1WI显示上述病灶呈显著不均匀强化征象(箭头所示)

Figure 1 Preoperative head MRI findings Axial T_1WI showed isointensity in left CPA and bilateral internal auditory canal (arrow indicates), adjacent left brachium pontis and brain stem were compressed (Panel 1a). Axial T_2WI showed slightly hyperintensity in the left CPA and bilateral internal auditory canal (arrow indicates), the left lesion compressed the ipsilateral pontine arm and cerebellum, and the left cerebellum had edema (Panel 1b). Axial fat suppression enhanced T_1WI showed significantly homogeneous enhancement (arrow indicates, Panel 1c).

部肿瘤切除前通过神经电生理监测分辨面神经,发现面神经被肿瘤推挤向腹侧,保护面神经并继续切除肿瘤;由于部分深部肿瘤与面神经粘连紧密并嵌入面神经,仔细分离与面神经粘连的肿瘤组织,切除后送检,最后小心磨除内听道后嵴,次全切除内听道内残留肿瘤。手术顺利,面神经解剖保留完好,术毕转至重症监护病房(ICU),予脱水降低颅内压、补液、抗感染等治疗。术后病理检查结果:大体标本观察,手术切除标本包含两种肿瘤组织,二者紧密相连,边界清晰。HE染色,神经鞘瘤细胞呈梭形,细胞排列疏密不均,部分胞核呈轻度异形性,部分淋巴细胞浸润;脑膜瘤细胞呈上皮样及梭形,呈"漩涡"样及"流水"样排列,可见散在砂粒体(图2a)。免疫组化染色(EnVision二步法),神经鞘瘤细胞胞核表达S-100蛋白(S-100),胞质表达波形蛋白(Vim),不表达孕激素受体(PR)、上皮膜抗原(EMA),Ki-67抗原标记指数约为1%(图2b);脑膜瘤细胞胞核表达PR,胞质表达Vim,胞膜表达EMA,不表达S-100,Ki-67抗原标记指数约为4%(图2c)。病理诊断为左侧脑桥小脑角碰撞瘤[神经鞘瘤与过渡型脑膜瘤(WHO Ⅰ级)]。患者术后恢复良好,听神经功能障碍未进一步加重,且未出现新发神经功能障碍。患者共住院19天,于2018年9月25日出院,出院时一般状况良好,无口服药物。出院4年(2022年9月7日)门诊复查,无特殊不适,头部MRI检查显示左侧内听道少量肿瘤残留,右侧内听道病变无明显变化,未见明确肿瘤复发及进展(图3)。

讨 论

颅内碰撞瘤系颅内同一部位发生的具有两种不同组织成分的肿瘤,形态学上无组织移行关系,临床罕见[1],其中主要为胶质瘤和脑膜瘤的颅内碰撞瘤[2-3]。听神经瘤是脑桥小脑角区最常见的良性肿瘤,又称前庭神经鞘瘤,是一种典型的神经鞘瘤,约占该部位全部肿瘤类型的80%,脑膜瘤占10%~15%[4-6],但发生于此区域的听神经瘤与脑膜瘤的碰撞瘤鲜有报道。脑桥小脑角区同时出现神经鞘瘤和脑膜瘤通常发生于Ⅱ型神经纤维瘤病等神经皮肤综合征患者中[7-8]。Ⅱ型神经纤维瘤病是一种罕见的常染色体显性遗传性疾病,由定位于染色体22q12.2的*NF2*基因变异所致,发病率约1/33 000,平均发病年龄为30岁[9-10]。Ⅱ型神经纤维瘤病累及中枢神经系统时常表现为双侧听神经瘤;在一级直系亲属罹患Ⅱ型神经纤维瘤病的遗传背景下,可表现为单侧听神经瘤合并胶质瘤、脑膜瘤、晶状体后包膜下浑浊或颅内钙化等疾病[9-11]。

目前有关碰撞瘤的病理生理学机制尚不十分明确,主要有以下几种学说:(1)肿瘤微环境学说。

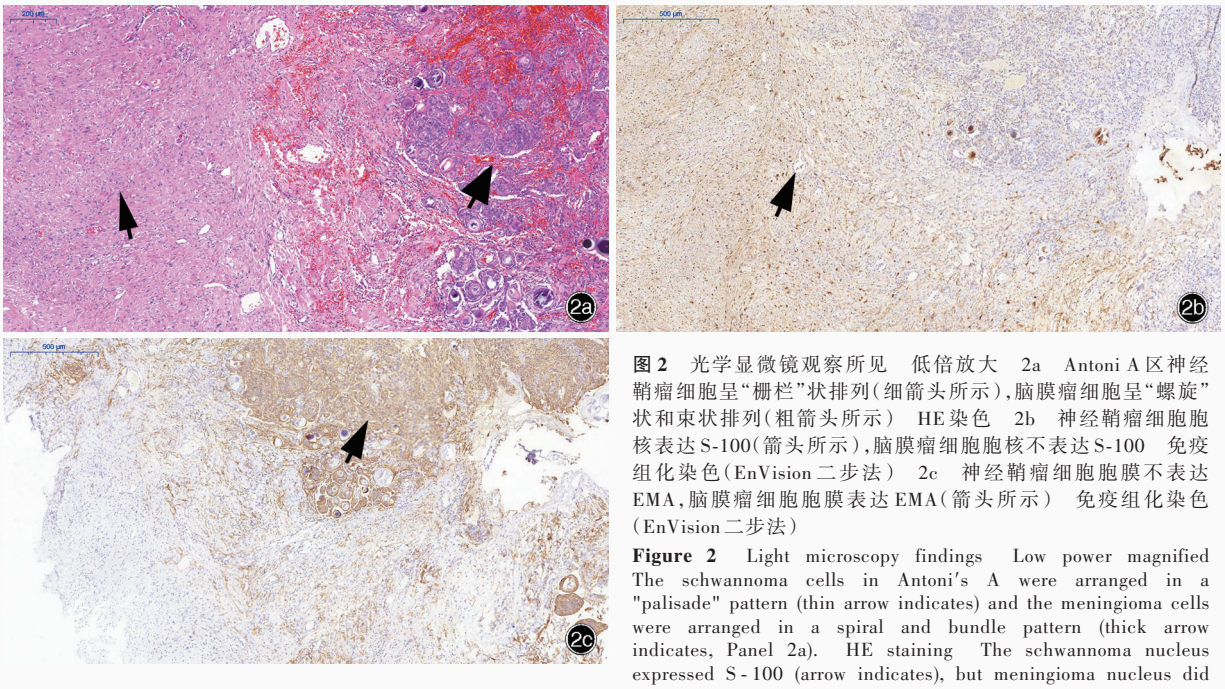

图2 光学显微镜观察所见 低倍放大 2a Antoni A区神经鞘瘤细胞呈"栅栏"状排列(细箭头所示),脑膜瘤细胞呈"螺旋"状和束状排列(粗箭头所示) HE染色 2b 神经鞘瘤细胞胞核表达S-100(箭头所示),脑膜瘤细胞胞核不表达S-100 免疫组化染色(EnVision二步法) 2c 神经鞘瘤细胞胞膜不表达EMA,脑膜瘤细胞胞膜表达EMA(箭头所示) 免疫组化染色(EnVision二步法)

Figure 2 Light microscopy findings Low power magnified The schwannoma cells in Antoni's A were arranged in a "palisade" pattern (thin arrow indicates) and the meningioma cells were arranged in a spiral and bundle pattern (thick arrow indicates, Panel 2a). HE staining The schwannoma nucleus expressed S-100 (arrow indicates), but meningioma nucleus did not express S-100 (Panel 2b). Immunohistochemical staining (EnVision) The schwannoma nucleus did not express EMA, but meningioma nucleus expressed (arrow indicates, Panel 2c). Immunohistochemical staining (EnVision)

一种肿瘤发生后通过改变周围微环境诱发另一种肿瘤[12-17],神经鞘瘤通过引起相邻脑膜反应性改变,促进脑膜瘤发生发展;表现为双侧听神经瘤的神经纤维瘤病患者蛛网膜增生较单纯散发性听神经瘤患者更旺盛,可能是诱发脑膜瘤的关键因素[10,18]。(2)肿瘤遗传学说。第二代测序技术(NGS)发现,定位于第22号染色体长臂的*merlin*基因为脑膜瘤关键抑癌基因,该基因变异与脑膜瘤发生密切相关。*merlin*基因通过调控Rac-PAK、EGFR-Ras-ERK、PI3K-Akt、FAK-Src等多种有丝分裂相关信号转导通路,活化Hippo-YAP信号转导通路,参与调控接触依赖抑制细胞增殖[19];此外,*merlin*基因可以与α-钙调素和Par-3蛋白在细胞黏附连接形成的初始阶段发挥作用,并与血管抑素结合蛋白(AMOT)相互作用,协助细胞黏附。研究表明,Ⅱ型神经纤维瘤病患者脑膜瘤组织中Wnt、EGFR和细胞黏附相关信号通路存在异常,同时在听神经瘤患者中发现*merlin*基因缺失或失活[20],因此脑膜瘤和听神经瘤可能在第22号染色体长臂的*merlin*基因变异中具有共同起源。(3)肿瘤发生学说。一种说法为碰撞瘤是由相同起源的间充质细胞差异分化形成两种不同类型的肿瘤细胞,最终发展成碰撞瘤[14,21-22];另一种说法为同一部位两种不同类型细胞在共同的致癌因素作用下发生癌变,最终发展为碰撞瘤[12,22]。(4)偶然并发学说。该学说认为碰撞瘤的形成是两种独立肿瘤在同一部位同时发生的一个巧合[23]。目前文献报道的碰撞瘤多为相应部位的常见肿瘤类型,由于该组织或器官相关肿瘤自身发病率高,因此发生碰撞的概率同样较高。(5)其他学说。研究发现,颅脑创伤、外科手术和放射治疗史可能是颅内碰撞瘤的潜在诱因。研究发现儿童时期接受放射治疗可显著增加神经鞘瘤发病率[24-26]。在Ron等[12]的研究中,共纳入1948-1960年在以色列接受放射治疗的10 834例儿童头癣患者,并以5392名未接受放射治疗的家族中其他成员作为对照,发现头癣患儿发生颅内神经鞘瘤(RR = 18.800, P = 0.014)及脑膜瘤(RR = 9.500, P = 0.038)的风险显著高于对照者,且放射治疗剂量与神经系统肿瘤发生风险存在剂量-反应关系。放射治疗史可能是本文患者潜在的危险因素,但遗憾的是未对患者及其家属进行全面的基因检测,具体病因仍未可知。

由于碰撞瘤的临床表现和影像学征象均无显著特异性,因此仅根据术前头部MRI检查难以对本文患者同一部位的两种肿瘤做出准确诊断,尤其是Ⅱ型神经纤维瘤病患者可出现颅内多部位、多种肿瘤类型共存[27-29]。影像学上,神经鞘瘤常呈圆形或

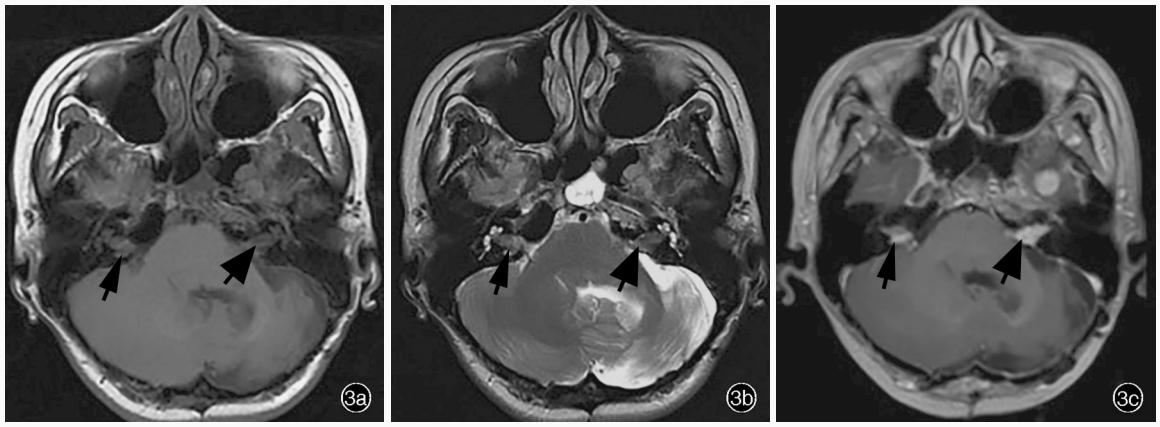

图3 出院4年头部MRI检查显示左侧脑桥小脑角脑膜瘤全切除(粗箭头所示),左侧听神经瘤近全切除,内听道沿面神经和前庭蜗神经走行部位少量肿瘤残留,右侧内听道病变无明显变化(细箭头所示) 3a 横断面T_1WI 3b 横断面T_2WI 3c 横断面抑脂增强T_1WI

Figure 3 Postoperative head MRI findings (September 7, 2022) showed gross-total resection of the left CPA meningioma (thick arrow indicates), sub-total resection of the left vestibular schwannoma, a small amount of residual tumor tissue in the internal auditory canal along the route of the facial acoustic nerve, and no change in the lesions of the right internal auditory canal compared with before (thin arrow indicates). Axial T_1WI (Panel 3a). Axial T_2WI (Panel 3b). Axial fat suppression enhanced T_1WI (Panel 3c).

椭圆形,以内听道为中心生长,并引起内听道扩大,体积较大的神经鞘瘤常见囊性变,钙化罕见[30-31];脑膜瘤则呈半圆或半椭圆形,基底较宽且多位于周围脑膜或颅底骨质,通常伴有"脑膜尾征",不以内听道为中心生长,不引起内听道扩大,其内可见钙化,部分可出现局部颅骨硬化增生[6,32];在T_1WI上,神经鞘瘤和脑膜瘤通常表现为等或稍低信号;在T_2WI上,神经鞘瘤表现为不均匀的高信号,而脑膜瘤则多表现为均匀的稍高信号;增强扫描后神经鞘瘤呈非均匀显著强化,而脑膜瘤多呈均匀中等强化[33-34]。本文患者术前影像学检查显示左侧脑桥小脑角区呈T_1WI等信号、T_2WI稍高信号,与既往研究相一致。然而,对于碰撞瘤这种空间相邻的病变,难以通过影像学检查鉴别,病理学检查仍是诊断的"金标准"。

随着现代显微外科手术、内镜技术、立体定向放射治疗技术、术前多模态影像学融合、术中电生理监测的进步,脑桥小脑角肿瘤的治疗方案日趋完善,并强调个体化治疗和多学科协作诊疗模式的重要性。尽管国内外均有采用立体定向放射外科治疗脑桥小脑角区肿瘤的报道,但对于体积较大的肿瘤,放射治疗后形成的水肿可能会导致颅内压升高,甚至出现脑疝;且深部肿瘤由于毗邻脑干、脑神经等重要结构,放射治疗引起的放射性损伤可导致严重的神经功能障碍,故外科手术目前仍是治疗脑桥小脑角肿瘤的主要方式[35-38]。神经影像导航和听觉脑干诱发电位实时监测等辅助手段可有效减少术中肿瘤切除过程中的神经副损伤,提高手术精准性和安全性[39]。本文患者由于右侧听神经瘤体积较小,无临床症状及手术指征,且如果单纯为切除肿瘤,术后易出现听力损失,故未行手术切除,仅行左侧脑桥小脑角肿瘤切除术。

综上所述,颅内碰撞瘤临床少见,脑桥小脑角区听神经瘤和脑膜瘤的碰撞瘤更为罕见,其临床症状及影像学表现与该部位常见肿瘤无显著差异,易被忽视,明确诊断仍需术后的组织病理学检查,临床医师及病理科医师应提高诊断与鉴别诊断的能力,早期进行积极治疗。

利益冲突 无

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·小词典·

中英文对照名词词汇(三)

微管相关蛋白tau
microtubule-associated protein tau(MAPT)

微血管减压术 microvascular decompression(MVD)

蜗神经动作电位 cochlear nerve action potential(CNAP)

无进展生存期 progression free survival(PFS)

细胞程序性死亡蛋白1
programmed cell death protein 1(PD1)

细胞程序性死亡蛋白配体1
programmed cell death protein ligand 1(PDL1)

细胞角蛋白 cytokeratin(CK)

细胞外信号调节激酶
extracellular signal-regulated kinase(ERK)

细胞周期蛋白依赖性激酶抑制基因2B
cyclin-dependent kinase inhibitor 2B(CDKN2B)

线粒体病 mitochondrial disease(MD)

线粒体脑肌病伴高乳酸血症和卒中样发作
mitochondrial encephalomyopathy with lactic academia and stroke-like episodes(MELAS)

线粒体隐性共济失调综合征
mitochondrial recessive ataxia syndrome(MIRAS)

相对脑血容量 relative cerebral blood volume(rCBV)

行为异常型额颞叶痴呆
behavioral variant frontotemporal dementia(bvFTD)

Ⅱ型神经纤维瘤病 neurofibromatosis type 2(NF2)

虚拟现实 virtual reality(VR)

血管内皮生长因子
vascular endothelial growth factor(VEGF)

血管内皮生长因子-A
vascular endothelial growth factor-A(VEGF-A)

血管内皮生长因子受体
vascular endothelial growth factor receptor(VEGFR)

亚急性坏死性脑脊髓病
sub-acute necrotizing encephalomyelitis(LS)

言语识别率 speech discrimination score(SDS)

岩静脉 petrosal vein(PV)

Leber遗传性视神经病
Leber's hereditary optic neuropathy(LHON)

N-乙酰天冬氨酸 N-acetyl-aspartate(NAA)

异柠檬酸脱氢酶1/2 isocitrate dehydrogenase 1/2(IDH1/2)

吲哚菁绿荧光血管造影术
indocyanine green angiography(ICGA)

婴儿型脊髓小脑性共济失调
infantile-onset spinocerebellar ataxia(IOSCA)

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

孕激素受体 progesterone receptor(PR)

运动诱发电位 motor-evoked potential(MEP)

中枢神经系统肿瘤分子信息与分类实践联盟-非WHO官方组织
Consortium to Inform Molecular and Practical Approaches to Central Nervous System Tumor Taxonomy-Not Official WHO(cIMPACT-NOW)

肿瘤微环境 tumor microenvironment(TME)

重症监护病房 intensive care unit(ICU)

椎动脉 vertebral artery(VA)

自动解剖分区 anatomical automatic labeling(AAL)

Kearns-Sayre综合征 Kearns-Sayre syndrome(KSS)

族错误率 family-wise error(FWE)