

右侧额叶转移性沙砾体型肺乳头状腺癌

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【摘要】 目的 报告 1 例临床罕见的右侧额叶转移性沙砾体型肺乳头状腺癌患者,结合文献探讨其临床病理学特点、诊断与鉴别诊断要点。**方法与结果** 男性患者,56 岁,临床表现为额枕部间歇性头痛。MRI 显示右侧额叶占位性病变,考虑脑膜瘤可能。术中可见右侧额叶肿瘤呈灰红色、质地较韧、边界清楚、血供丰富。组织学形态观察,肿瘤组织呈乳头状结构,胞质嗜酸性,胞核呈圆形或卵圆形,可见小的红核仁,肿瘤组织和肿瘤间质中可见大量沙砾体形成;免疫组织化学染色,肿瘤细胞弥漫性表达细胞角蛋白(CK)、上皮膜抗原、CK19、甲状腺转录因子-1 和 Napsin A 蛋白,灶性表达 P53, Ki-67 抗原标记指数为 5%~10%;不表达胶质纤维酸性蛋白、S-100 蛋白、甲状腺球蛋白、Galectin-3 蛋白、孕激素受体、波形蛋白等标志物。结合胸部¹⁸F-FDG-PET CT 显像,最终病理诊断为(右侧额叶)转移性沙砾体型肺乳头状腺癌。术后辅以放射治疗和药物化疗,随访 12 个月,肿瘤无复发。**结论** 中枢神经系统转移性沙砾体型肺乳头状腺癌临床罕见,应详细了解病史,并注意与乳头状型脑膜瘤、脉络丛乳头状瘤、乳头状型室管膜瘤、乳头状型胶质神经元肿瘤和转移性甲状腺乳头状癌等相鉴别,以免误诊或漏诊。

【关键词】 腺癌,乳头状; 肺肿瘤; 肿瘤转移; 额叶; 免疫组织化学; 病理学

Pulmonary papillary adenocarcinoma with psammoma bodies metastasis to right frontal lobe

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【Abstract】 Objective To investigate the clinical manifestations and pathological characteristics of pulmonary papillary adenocarcinoma with psammoma bodies metastasis to right frontal lobe of brain. **Methods** The clinical manifestations, pathological features and differential diagnosis were studied in one case of pulmonary papillary adenocarcinoma with psammoma bodies metastasis to right frontal lobe. Related literatures were also reviewed. **Results** A 56-year-old male suffered from intermittent headache for 3 years in fronto-occipital region without significant incentives. Cranial MRI examination revealed a space-occupying lesion in right frontal lobe, which was considered as meningioma. In operation, the tumor located in the right frontal lobe was tough and red-grey in color, with clear boundary and abundant blood supply. Histopathological examination revealed the tumor was arranged in papillary pattern. The tumor cells were large, with eosinophilic cytoplasm, round or oval nuclei and small red nucleoli. Especially, a plenty of psammoma bodies were found in tumor tissue and mesenchymal tissue. Immunohistochemical staining found that the tumor cells were positively expressed for cytokeratin (CK), epithelial membrane antigen (EMA), CK19, thyroid transcription factor-1 (TTF-1) and Napsin A, and showed focal positive expression of P53. Ki-67 labeling index was 5%–10%. The tumor cells were negative for glial fibrillary acidic protein (GFAP), S-100 protein (S-100), thyroglobulin (TG), Galectin-3 protein, progesterone receptor

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(PR) and vimentin (Vim). Combined with the results of chest ^{18}F -FDG-PET CT, the final diagnosis was pulmonary papillary adenocarcinoma with psammoma bodies metastasis to right frontal lobe. The patient underwent auxiliary radiotherapy and chemotherapy after operation. The patient was followed for 12 months and no recurrence was seen. **Conclusions** This case is very rare. Understanding the patient's history and differentiating from other primary intracalvarium tumors is one of the key steps to give the right pathological diagnosis and clinical therapy. In order to avoid misdiagnosis, the diagnosis needs to be differentiated from other primary intracalvarium tumors, including papillary meningioma, papillary tumor of choroid plexus, papillary ependymoma, papillary glioneuronal tumors as well as metastatic papillary thyroid carcinoma.

【Key words】 Adenocarcinoma, papillary; Lung neoplasms; Neoplasm metastasis; Frontal lobe; Immunohistochemistry; Pathology

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肺乳头状腺癌约占肺腺癌的 20%，而伴大量沙砾体形成的肺腺癌少见，尤其是沙砾体型肺乳头状腺癌临床罕见^[1-2]。转移至中枢神经系统后，病理学特征使之易与其他原发性中枢神经系统肿瘤相混淆。国内尚未见此类病例的详细报道，山东大学附属省立医院明确诊断 1 例右侧额叶转移性沙砾体型肺乳头状腺癌患者，笔者拟根据临床诊断与治疗经过，结合文献对其临床病理学特征进行分析，以为临床诊断提供思路。

病历摘要

患者 男性，56 岁。因头痛 3 年余，加重 1 个月，于 2014 年 1 月 9 日入院。患者于 3 年前无明显诱因出现头痛，以额枕部明显，间歇发作，无眩晕，无恶心、呕吐，无癫痫发作；约 1 年前出现嗅觉减退；约 1 个月前头痛症状明显加重。患者自发病以来，神志清楚、精神、睡眠尚可、食欲不佳、体重无明显变化、大小便正常。

既往史、个人史及家族史 均无特殊。

体格检查 患者体温 36.4℃，呼吸 17 次/min，脉搏 80 次/min，血压 136/80 mm Hg (1 mm Hg = 0.133 kPa)。神志清楚，精神尚可，查体合作。双侧瞳孔等大、等圆，直径约 4 mm，对光反射灵敏；双眼视力无明显下降，粗测双眼视野无缺损。双侧鼻唇沟对称，无口角歪斜，无听力下降。四肢肌力 5 级、肌张力增高，四肢腱反射亢进，双侧 Babinski 征阴性。颈部稍抵抗。

辅助检查 血尿便常规均于正常值范围。肝肾功能试验、电解质和凝血四项均于正常值范围。肿瘤标志物检查无明显异常。头部 MRI 扫描右侧

额叶可见 2 个病灶，最大横截面积分别为 5.70 cm × 4.70 cm 和 5.10 cm × 3.90 cm，病灶边缘呈浅分叶状，分别与大脑镰和蝶骨关系密切，T₁WI 呈等信号、其内呈斑片状低信号，T₂WI 呈等信号、其内呈稍高或稍低混杂信号，周围可见大片状长 T₁、长 T₂ 水肿区，边界不清；增强扫描病灶呈明显不均匀强化，右侧侧脑室受压变窄，中线结构向左侧移位，并可见大量沙砾体样钙化，符合脑膜瘤表现(图 1)。临床诊断：右侧额叶脑膜瘤，不排除中枢神经系统转移瘤。

诊断与治疗经过 入院后常规进行术前检查，临床考虑为右侧额叶脑膜瘤，于 2011 年 11 月 8 日行右侧额叶肿瘤切除术。采用双侧额叶冠状切口，于额上回后部近中线处切开，深入 2 cm 可见一肿瘤组织，呈灰红色、质地较韧、边界尚清、无包膜、血供丰富，含大量沙砾体样钙化，肿瘤内侧达大脑镰，与周围脑组织无粘连，手术全切除肿瘤。另一肿瘤组织位于距额极 3 cm 处，呈灰红色、质地较软、边界尚清、无包膜、血运丰富，肿瘤后方达垂体柄前，与周围脑组织无粘连，手术全切除肿瘤。术后行组织病理学检查。(1)大体标本观察：手术切除的右侧额叶肿瘤标本为不规则破碎组织块，大小约为 4.50 cm × 3.50 cm × 3.00 cm，表面略粗糙，切面呈灰白、灰红色，质地较韧，边界清楚；手术切除的近鞍区肿瘤标本为不规则破碎组织块，大小约 3 cm × 2 cm × 1 cm，表面粗糙，切面呈灰白、灰红色，质地柔软，边界清楚。经体积分数为 4% 中性甲醛溶液固定、石蜡包埋、制备组织切片，行 HE 染色和免疫组织化学染色。(2)HE 染色：光学显微镜观察，肿瘤组织以乳头状排列方式为主(图 2a, 2b)，由中等大小的上皮样细胞围绕纤维血管组成。肿瘤细胞呈立方形或圆

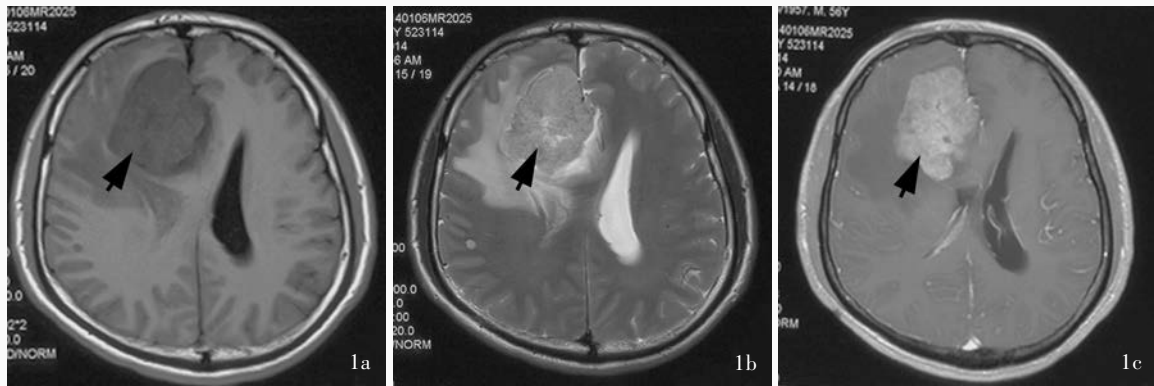


图1 头部MRI检查所见 1a 横断面T₁WI显示,右侧额叶不规则病灶呈等信号,其内可见斑片状低信号(箭头所示) 1b 横断面T₂WI显示,右侧额叶病灶以等信号为主(箭头所示) 1c 横断面增强T₁WI显示,右侧额叶病灶呈明显不均匀强化(箭头所示)

Figure 1 MRI examination findings. Axial T₁WI showed the lesion with equisignal in right frontal lobe, and patchy low-density signal could be seen within the lesion (arrow indicates, Panel 1a). Axial T₂WI showed equisignal of the lesion in right frontal lobe (arrow indicates, Panel 1b). Axial enhanced T₁WI showed heterogeneous enhancement of the lesion in right frontal lobe (arrow indicates, Panel 1c).

柱状,胞质丰富,呈嗜酸性、部分呈嗜双色性,胞核呈圆形或卵圆形、多位于细胞中央,染色质呈粗颗粒状,可见小的红核仁(图2c);细胞异型性明显,核仁清楚,部分细胞可见核沟(图2d);细胞无坏死,核分裂象可见。肿瘤组织和间质中可见大量沙砾体结构,直径50~70 μm,嗜碱性,呈同心圆层状排列,切面似“洋葱皮”样(图2e,2f)。沙砾体呈细颗粒状,分布不均匀,部分区域集中呈片状,甚至覆盖肿瘤细胞。(3)免疫组织化学染色:采用SP二步法,检测用细胞角蛋白(CK)、胶质纤维酸性蛋白(GFAP)、上皮膜抗原(EMA)、S-100蛋白(S-100)、波形蛋白(Vim)、突触素(Syn)、孕激素受体(PR)、CK19、Galectin-3蛋白(Galectin-3)、甲状腺球蛋白(TG)、甲状腺转录因子-1(TTF-1)、P53和Napsin A蛋白(Napsin A)均购自北京中杉金桥生物技术有限公司,Ki-67抗原由福州迈新生物技术有限公司提供。免疫组织化学检测试剂盒和二氨基联苯胺(DAB)显色试剂盒为北京中杉金桥生物技术有限公司产品。结果显示,肿瘤细胞弥漫性表达CK(图3a)、EMA(图3b)、TTF-1(图3c)和NapsinA(图3d),灶性表达P53(图3e),不表达GFAP和S-100等神经源性标志物、TG和Galectin-3等甲状腺乳头状癌标志物,以及PR和Vim,Ki-67抗原标记指数为5%~10%(图3f)。病理诊断:(右侧额叶)转移性沙砾体型乳头状腺癌,可能来源于肺。

术后行¹⁸F-FDG-PET CT重点扫描甲状腺和肺

部,双肺纹理增多,其内可见多发斑片状、条索状和毛玻璃样影,以左肺显著;右肺下叶前基底段近斜裂处可见2.40 cm×1.30 cm大小结节,形态欠规则,相邻肺叶间裂牵拉、移位;肺段以上支气管通畅;可见¹⁸F-FDG摄取增高的核素凝集热点(图4),提示双肺炎症性改变,右肺下叶占位性病变,考虑肺癌。患者拒绝行肺组织穿刺活检术。最终病理诊断:(右侧额叶)转移性沙砾体型乳头状腺癌,结合临床和免疫表型考虑原发肿瘤为肺癌。术后辅助放射治疗和药物化疗,随访至今12个月,肿瘤无复发。

讨 论

肺癌脑转移发生率居中枢神经系统转移性肿瘤首位。肺乳头状腺癌是较少见的肺腺癌类型、约占20%,女性多于男性。组织学形态观察,肿瘤组织由典型乳头状结构组成,肿瘤细胞围绕纤维血管排列。有文献报道,该肿瘤起源于Ⅱ型肺泡上皮细胞^[1-2]。其生物学行为较贴壁型和腺泡型肺腺癌差,术后复发率和淋巴结转移率则高于其他类型,易发生包括中枢神经系统在内的远隔转移。伴大量沙砾体形成的肺腺癌尤其是肺乳头状腺癌临床十分罕见,目前仅报道5例患者。发生转移者组织病理学特征不易与其他部位伴沙砾体形成的乳头状腺癌相鉴别,转移至中枢神经系统者不易与脉络丛乳头状瘤和乳头状型脑膜瘤相鉴别。目前,国内外均未见颅内转移性沙砾体型乳头状腺癌的详细报道。

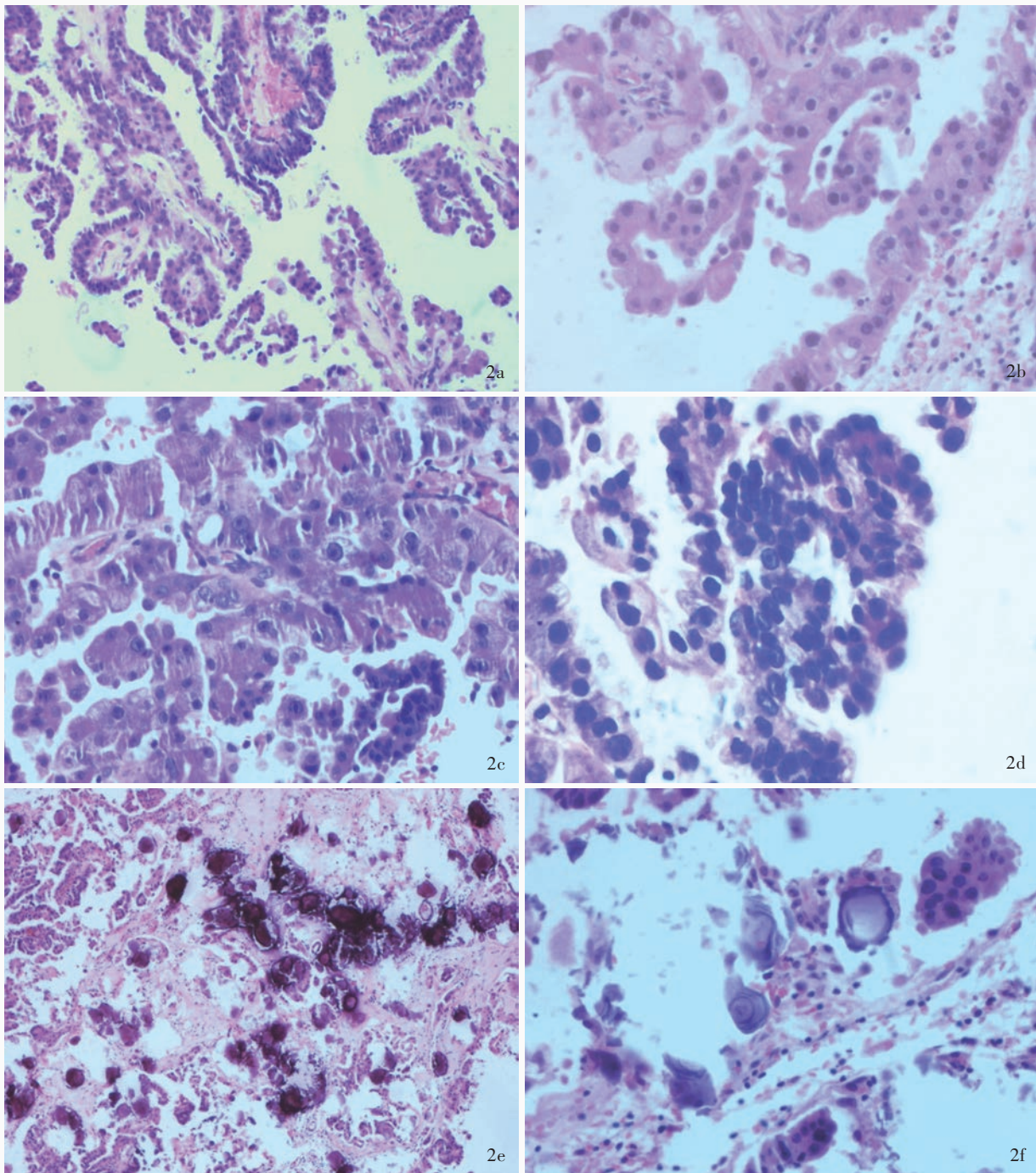


图 2 光学显微镜观察所见 HE 染色 2a 肿瘤组织以乳头状排列方式为主 $\times 200$ 2b 可见乳头状结构区域 $\times 400$ 2c 肿瘤细胞呈立方形或圆柱状,胞质丰富,呈嗜酸性、部分嗜双色性,胞核呈圆形或卵圆形、多位于细胞中央,染色质呈粗颗粒状,可见小的红核仁 $\times 400$ 2d 部分肿瘤细胞可见核沟 $\times 400$ 2e 肿瘤组织和肿瘤间质中可见大量沙砾体结构,直径 $50 \sim 70 \mu\text{m}$,嗜碱性 $\times 100$ 2f 沙砾体结构呈同心圆层状排列,切面似“洋葱皮”样 $\times 400$

Figure 2 Optical microscopy findings. HE staining Tumor cells were in papillary pattern (Panel 2a). $\times 200$ Papillary pattern could be seen (Panel 2b). $\times 400$ The tumor cells were cubiform or columned, with abundant eosinophilic cytoplasm, round or oval nuclei located in the center of cells, coarse grained chromatin and small red nucleoli (Panel 2c). $\times 400$ Some tumor cells showed nuclear grooves (Panel 2d). $\times 400$ Plenty of basophilic psammoma bodies could be seen in tumor tissue and mesenchymal tissue with diameter $50 \sim 70 \mu\text{m}$ (Panel 2e). $\times 100$ Psammoma bodies were arranged in concentric layered pattern as "onion" section (Panel 2f). $\times 400$

沙砾体是指肿瘤组织中直径 $50 \sim 70 \mu\text{m}$ 的病理性钙化灶,呈同心圆层状排列,切面似“洋葱皮”

样,因常为多枚嗜碱性细颗粒,如散沙状,故称沙砾体。目前认为其形成机制是继发于肿瘤细胞坏死

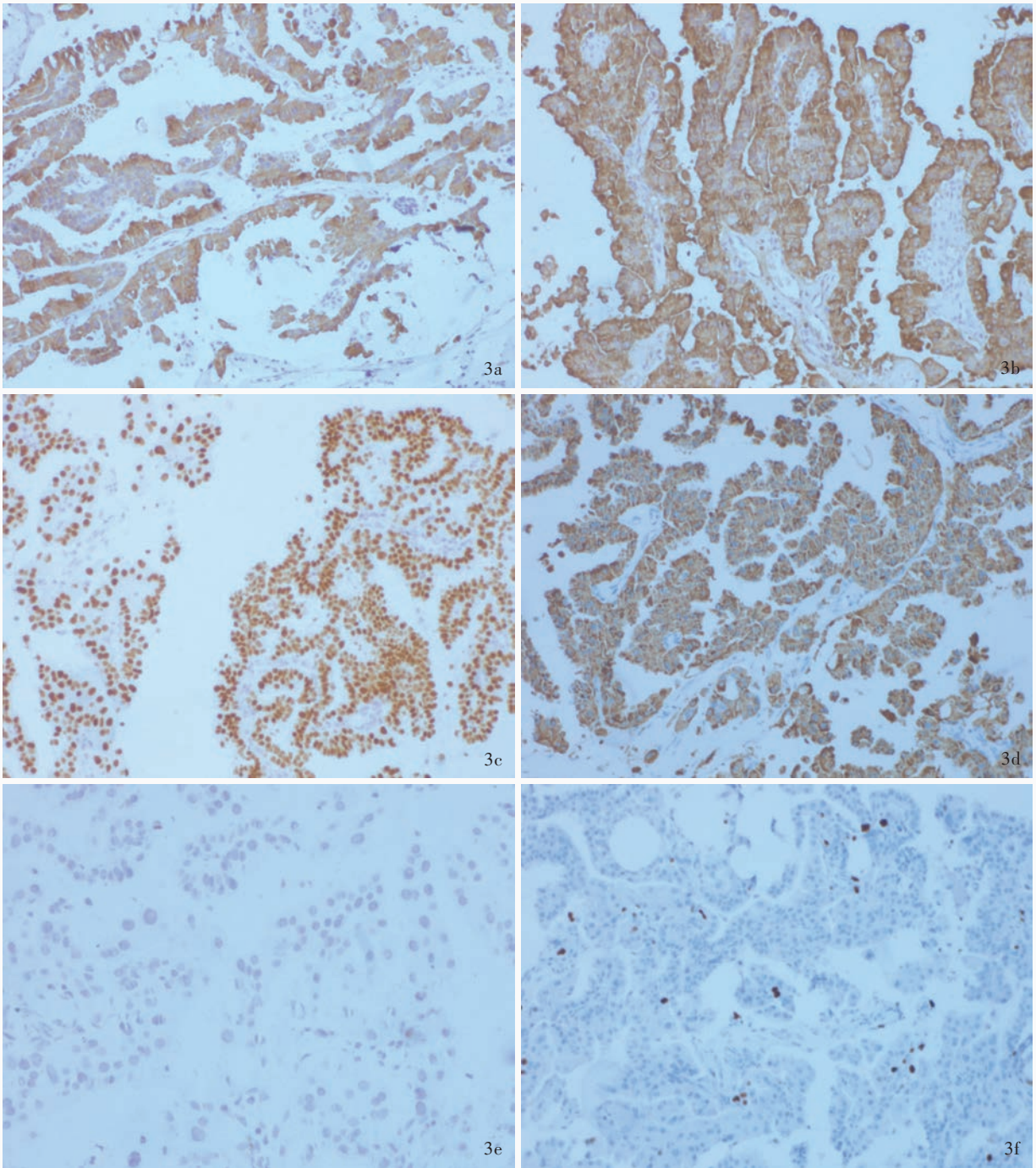


图 3 光学显微镜观察所见 免疫组织化学染色(SP 二步法) ×400 3a 肿瘤细胞胞膜和胞质弥漫性表达CK 3b 肿瘤细胞胞膜和胞质弥漫性表达EMA 3c 肿瘤细胞胞核弥漫性表达TTF-1 3d 肿瘤细胞胞质弥漫性表达Napsin A 3e 肿瘤细胞胞核灶性表达P53 3f Ki-67抗原标记指数为5%~10%

Figure 3 Optical microscopy findings. Immunohistochemical staining (SP) ×400 Tumor cells were diffusely positive for CK in membrane and cytoplasm (Panel 3a). Tumor cells were diffusely positive for EMA in membrane and cytoplasm (Panel 3b). TTF-1 expression was diffusely positive in nuclei of tumor cells (Panel 3c). Napsin A was diffusely positive in cytoplasm of tumor cells (Panel 3d). P53 protein was focally positive in part of nuclei (Panel 3e). Ki-67 labeling index was 5%–10% (Panel 3f).

或肿瘤细胞释放至局部的代谢产物继发的营养不良性钙化^[3]。伴大量沙砾体形成的肿瘤包括甲状腺乳头状癌、卵巢和腹膜浆液性肿瘤、脑膜瘤、促结缔

组织增生性小圆细胞肿瘤、乳头状肾细胞癌和肺乳头状腺癌等,以前三者最为常见,可以作为肿瘤诊断的组织学形态依据之一。目前,对于肿瘤中出现

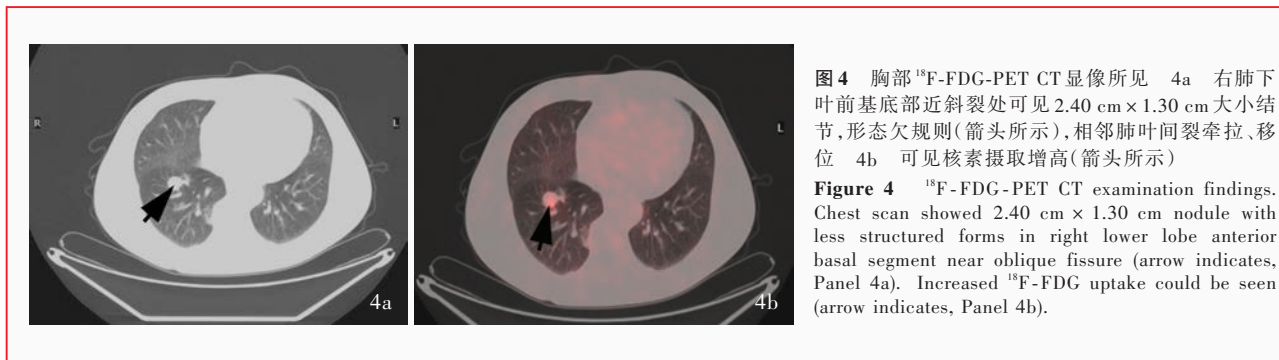


图4 胸部¹⁸F-FDG-PET CT显像所见 4a 右肺下叶前基底部近斜裂处可见2.40 cm × 1.30 cm大小结节,形态欠规则(箭头所示),相邻肺叶间裂牵拉、移位 4b 可见核素摄取增高(箭头所示)

Figure 4 ¹⁸F-FDG-PET CT examination findings. Chest scan showed 2.40 cm × 1.30 cm nodule with less structured forms in right lower lobe anterior basal segment near oblique fissure (arrow indicates, Panel 4a). Increased ¹⁸F-FDG uptake could be seen (arrow indicates, Panel 4b).

沙砾体与预后的关系尚不确定^[4-5],Das^[6]认为,沙砾体的存在可以导致肿瘤细胞坏死和肿瘤生长阻滞,因此沙砾体形成是恶性肿瘤具有良好生物学行为的指征。然而,伴大量沙砾体形成的甲状腺弥漫硬化型乳头状癌是易发生淋巴结和肺转移的预后较差的亚型之一^[7-8]。

含少量或局灶性沙砾体结构的原发性中枢神经系统肿瘤包括脑膜瘤、少突胶质细胞瘤和(或)少突-星形细胞瘤、室管膜瘤、室管膜下室管膜瘤、脉络丛乳头状瘤、神经节细胞胶质瘤、中枢神经细胞瘤和胚胎发育不良性神经上皮肿瘤(DNT),而含大量沙砾体结构者罕见^[9-10]。以乳头状结构为主的原发性中枢神经系统肿瘤包括乳头状型室管膜瘤、脉络丛肿瘤、乳头状型胶质神经元肿瘤(PGNT)、松果体区乳头状肿瘤和乳头状型脑膜瘤。同时含沙砾体和乳头状结构的原发性中枢神经系统肿瘤有脉络丛乳头状瘤、乳头状型室管膜瘤和乳头状型脑膜瘤。由于转移性沙砾体型肺乳头状腺癌与上述肿瘤在组织形态学上较为相似且免疫组织化学染色TTF-1表达阳性而难以鉴别,因此,详细的病史询问、完善的实验室检查和必要的免疫组织化学染色对诊断与鉴别诊断十分必要。

转移性沙砾体型肺乳头状腺癌的组织学形态、免疫表型与原发性中枢神经系统肿瘤有重叠,亦与其他部位转移癌相似,临床较易误诊和漏诊,应注意与以下肿瘤相鉴别。(1)乳头状型脑膜瘤:属WHO III级,好发于儿童和青年,临床极罕见。肿瘤组织乳头状结构不十分清晰,大部分肿瘤细胞围绕血管周围形成假“菊形团”样结构,沙砾体少见。免疫组织化学染色,肿瘤细胞表达EMA、PR和Vim,灶性表达S-100^[11],也有部分肿瘤组织伴腺样分化^[12-13]。该例患者年龄偏大,组织学形态表现为乳头状结构和大量沙砾体,肿瘤细胞胞质和胞核分别弥漫性表

达Napsin A和TTF-1可资鉴别。(2)脉络丛乳头状瘤:好发于儿童,以脑室和脑桥小脑角常见,极少数异位肿瘤可发生于鞍上和脑实质,并可沿脑脊液播散而呈多发性,易与转移癌相混淆。组织学形态为立方或柱状上皮细胞围绕纤细纤维血管,胞核呈圆形或卵圆形,位于基底部,偶见嗜酸性、黏液变性和腺管样结构的肿瘤细胞,并可见大量沙砾体,甚至覆盖肿瘤细胞。免疫组织化学染色,肿瘤细胞表达Vim、S-100和GFAP,部分表达CK和癌胚抗原(CEA)^[14-15]。虽然该例患者组织学形态和免疫组织化学染色与脉络丛乳头状瘤极为相似,但肺癌标志物Napsin A表达阳性,且其发病部位非脉络丛乳头状瘤好发部位,尽管亦有脉络丛乳头状瘤异位生长的报道,但需排除其他肿瘤后方予考虑。(3)乳头状型室管膜瘤:可发生于任何年龄阶段,好发于脑室系统,少数发生于脑室外。组织学形态可见典型血管周围假“菊形团”样和室管膜“菊形团”样结构,上皮细胞呈线样排列,可见被覆平整、连接紧密的单层立方肿瘤细胞,伴大量沙砾体形成^[16]。免疫组织化学染色,肿瘤细胞表达GFAP、S-100和Vim,点状和环状表达EMA,部分表达CK和TTF-1。二者均有沙砾体和乳头状结构,且均表达TTF-1,不易鉴别。该例患者组织学形态未见典型假“菊形团”样结构;免疫组织化学染色肿瘤细胞GFAP、S-100呈阴性,Napsin A呈弥漫性阳性,可资鉴别。(4)乳头状型胶质神经元肿瘤:属WHO I级,以颞叶多发。由GFAP表达阳性的扁平形和立方星形胶质细胞围绕透明变性的血管形成假乳头状结构,以及突触素(Syn)表达阳性的乳头状和片状神经元组成,无沙砾体结构。免疫组织化学染色,肿瘤细胞GFAP和少突胶质细胞转录因子-2(Olig-2)表达阳性,同时表达神经元核抗原(NeuN)。该例患者组织学形态和免疫组织化学染色均与之不符^[17]。(5)转移性甲状腺

乳头状癌:近年来,甲状腺乳头状癌发病率不断升高,发生中枢神经系统转移者可同时出现乳头状和沙砾体结构,肿瘤细胞呈立方形或圆柱状,胞核呈“毛玻璃”样并可见核沟,排列重叠。二者均弥漫性表达TTF-1。该例患者肿瘤细胞弥漫性表达Napsin A,不表达TG,且PET-CT扫描可见肺部占位性病变更,可资鉴别。(6)转移性卵巢浆液性腺癌:二者组织学形态相似,免疫组织化学染色可资鉴别。

转移性沙砾体型肺乳头状腺癌患者中位生存期较原发性中枢神经系统肿瘤患者短,预后不良。因此,密切随访、监测神经功能变化,可提示临床医师尽早发现发生远隔部位转移的肿瘤,以尽早明确诊断,选择合理治疗方案。该例患者手术全切除肿瘤后,随访12个月无复发。转移性沙砾体型肺乳头状腺癌的生物行为及其对预后的影响尚待更多的病例观察和进一步的深入研究。

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下期内容预告 本刊2015年第7和8期报道专题为痴呆,重点内容包括:世界阿尔茨海默病发展现状;路易体痴呆百年史;PIN1对阿尔茨海默病的影响;行为异常型额颞叶痴呆研究进展;高血压与认知障碍;阿尔茨海默病各类PET分子探针研究进展;阿尔茨海默病:从临床诊断标准到神经病理诊断标准的进展和重塑;阿尔茨海默病药物联合治疗研究进展;尼莫地平治疗血管性痴呆疗效与安全性系统评价;轻度认知损害临床特征、诊断标准和筛查技术的循证医学研究;Cog-12对高龄老年人认知功能障碍的预测价值;阿尔茨海默病和轻度认知损害静息态fMRI默认网络研究;步态参数与阿尔茨海默病相关性研究;尿液神经微丝蛋白表达变化对痴呆的诊断价值探讨;交替流畅性试验对识别轻度认知损害与阿尔茨海默病的作用;艾地苯醌与多奈哌齐治疗阿尔茨海默病疗效比较;¹⁸F-FDG PET和¹¹C-PIB PET显像对后部皮质萎缩早期诊断价值探讨;阿尔茨海默病与血管性痴呆血浆同型半胱氨酸、尿酸和C-反应蛋白表达研究;慢性应激诱发APP/PS-1双转基因小鼠认知功能障碍;情绪对轻中度帕金森病患者认知功能的影响;轻度认知损害患者事件相关电位P300波随访研究;新编痴呆自调查问卷及其在痴呆筛查中的应用