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基于基因诊断的儿童原发性弥漫性软脑膜黑色素瘤病一例并文献复习

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摘　要

目的：报道儿童原发性弥漫性软脑膜黑色素瘤病(PDLM)的临床特征，探讨基因检测在本病诊断中的核心价值及靶向治疗的研究前景。方法：回顾1例经手术活检、病理及基因检测确诊的儿童PDLM临床资料，并系统复习相关文献。结果：本例11岁男性患儿以头痛、呕吐为主要表现，影像学示双侧脑膜弥漫增厚强化，手术活检病理示肿瘤细胞富含黑色素，免疫组化Melan-A(+)、S-100(+)、SOX-10(+)，基因检测提示NRAS Q61R突变(突变频率84.7%)。患儿确诊后保守治疗，2个月后死亡。结论：PDLM临床罕见、侵袭性强，儿童患者缺乏特异性表现易误诊，脑膜活检联合基因检测是确诊关键；NRAS为儿童PDLM核心突变基因，以MEK抑制剂为核心的靶向联合治疗为该病提供新方向，需进一步临床研究验证疗效。

关键词

原发性弥漫性软脑膜黑色素瘤病，儿童，基因诊断，NRAS突变，靶向治疗

Genetic Diagnosis-Based Management of Primary Diffuse Leptomeningeal Melanomatosis in a Pediatric Patient: A Case Report and Literature Review

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Abstract

Objective: To investigate the clinical characteristics of primary diffuse leptomeningeal melanomatosis (PDLM) in a pediatric patient and to elucidate the pivotal role of genetic testing in diagnosis, as well as the potential of targeted therapy. Methods: The clinical data of a pediatric case confirmed by surgical biopsy, histopathology, and genetic testing were retrospectively analyzed, and a systematic literature review was conducted. Results: An 11-year-old male patient presented with headache and vomiting. Neuroimaging revealed diffuse thickening and enhancement of the bilateral meninges. Histopathological examination of the surgical biopsy showed melanin-rich tumor cells, with immunohistochemistry positive for Melan-A, S-100, and SOX-10. Genetic testing identified an NRAS Q61R mutation with a variant allele frequency of 84.7%. The patient received conservative treatment and died two months after diagnosis. Conclusion: PDLM is a rare and highly aggressive entity. Pediatric patients often present with non-specific symptoms, leading to a high risk of misdiagnosis. Meningeal biopsy combined with genetic testing is essential for a definitive diagnosis. NRAS is a core driver gene in pediatric PDLM. MEK inhibitor-based combination targeted therapy may offer a novel treatment strategy, warranting further clinical investigation.

Keywords

Primary Diffuse Leptomeningeal Melanomatosis, Pediatric, Genetic Diagnosis, NRAS Mutation, Targeted Therapy

1. 背景

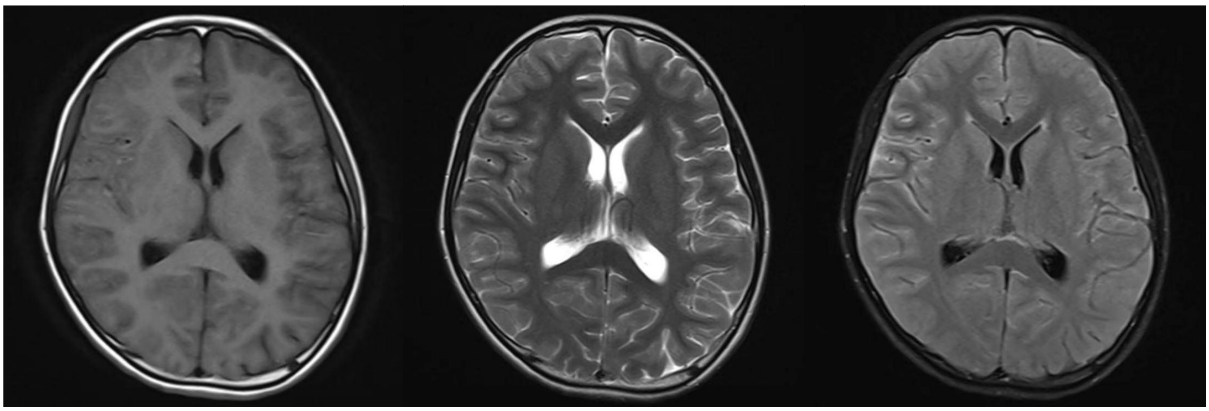
原发性弥漫性软脑膜黑色素瘤病(PDLM)是起源于软脑膜黑色素细胞的中枢神经系统罕见高度恶性肿瘤，全球发病率约每 2000 万人中 1 例，儿童患者更罕见，占儿童神经肿瘤的 0.1% [1] [2]。其发病与胚胎神经嵴来源黑色素母细胞异常增殖恶性转化相关，肿瘤细胞弥漫浸润软脑膜及蛛网膜下腔，无颅外转移，临床误诊率高[3]。

PDLM 临床表现缺乏特异性，以颅内高压症状为主，易与结核性脑膜炎、脑膜瘤等混淆[4]。传统诊断依赖脑膜活检 + 免疫组化，但部分病例病理特征不典型，需基因检测明确分子分型[5]。研究显示，成人 PDLM 以 GNAQ、GNA11 突变为特征，儿童则以 NRAS Q61K/R 和 BRAF V600E 突变为主，其中 NRAS 激活突变占儿童病例的 20%~30% [6] [7]。

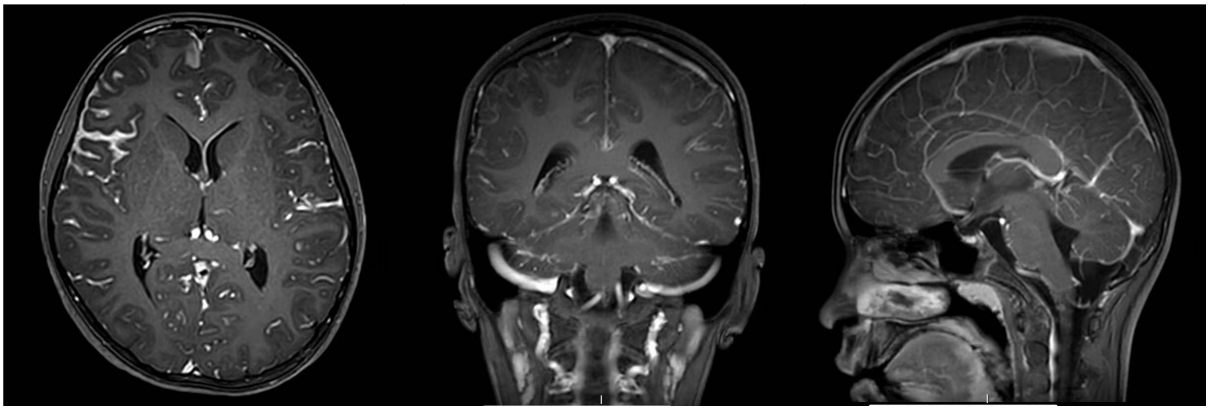
目前 PDLM 治疗以手术活检 + 对症支持为主，放化疗效果有限，儿童中位生存期仅 5~7 个月[8]。随着分子诊断技术发展，靶向突变基因的精准治疗成为研究热点，尤其是 NRAS 突变相关的 MEK/ERK 通路抑制剂，为改善患儿预后提供了新可能。本文通过分析 1 例经基因检测确诊的儿童 PDLM 病例，结合文献探讨基因诊断价值及靶向治疗前景，为临床诊疗提供参考。

2. 病历资料

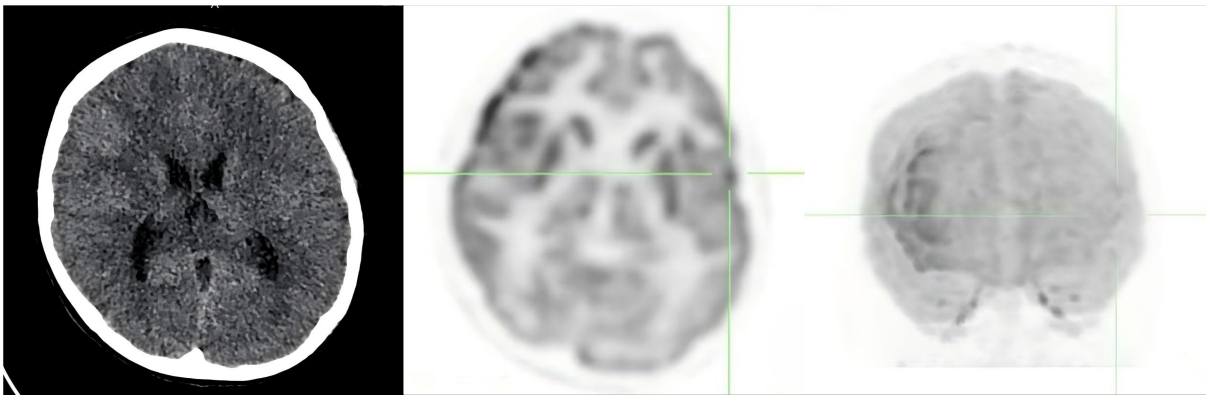
患者，男，11 岁，因“头痛、头晕伴呕吐 1 月余，癫痫发作 2 次”入院。患儿无明显诱因出现间断头痛，右侧额颞部为主，伴喷射性呕吐，每日数次，外院予拉考沙胺抗癫痫后未再发作。既往体健，无皮肤黑色素瘤病史。



(a) (b) (c)



(d) (e) (f)



(g) (h) (i)

Figure 1. Male, 11 years old, with PDLM. MRI with DWI demonstrated isointense to slightly hypointense signals on T1WI and hyperintense signals on T2WI and FLAIR in the cortices of bilateral cerebral and cerebellar hemispheres, predominantly involving the right frontotemporal lobe. These findings were consistent with the imaging features of hypopigmented PDLM (a)~(c). Contrast-enhanced gadolinium MRI in axial, coronal and sagittal planes revealed diffuse meningeal thickening and enhancement in bilateral cerebral and cerebellar hemispheres ((d)~(f)). Bone-window CT showed scattered patchy slightly high-density lesions in bilateral frontal lobes and right temporal lobe (g). 18F-FDG PET-CT demonstrated patchy abnormal radiotracer uptake in bilateral frontotemporal lobes, left occipital lobe, interhemispheric fissure and tentorium cerebelli (h)~(i)
图 1. 男，11 岁，原发性弥漫性软脑膜黑色素瘤病。MRI + DWI 示双侧大脑半球及小脑半球皮层 T1WI 等/稍低信号、T2WI 及 FLAIR 高信号，右侧额颞叶为著。符合低色素亚型的 PDLM 病变表现图 (a)~(c)。钆增强扫描轴位、冠状位、矢状位可见双侧大脑半球及小脑半球多发脑膜增厚并强化图 (d)~(f)。CT 骨窗显示双侧额叶、右侧颞叶散在斑片状稍高密度影图 (g)。18F-FDG PET-CT 示双侧额颞叶、左侧枕叶、大脑纵裂池区、小脑幕区斑片状异常显像剂浓聚图 (h)~(i)

体格检查：神志清，双侧瞳孔等大等圆，直径 3.0 mm，对光反射灵敏，双侧肢体肌力 V 级，肌张力正常，病理反射未引出，无皮肤色素痣及异常黑斑。

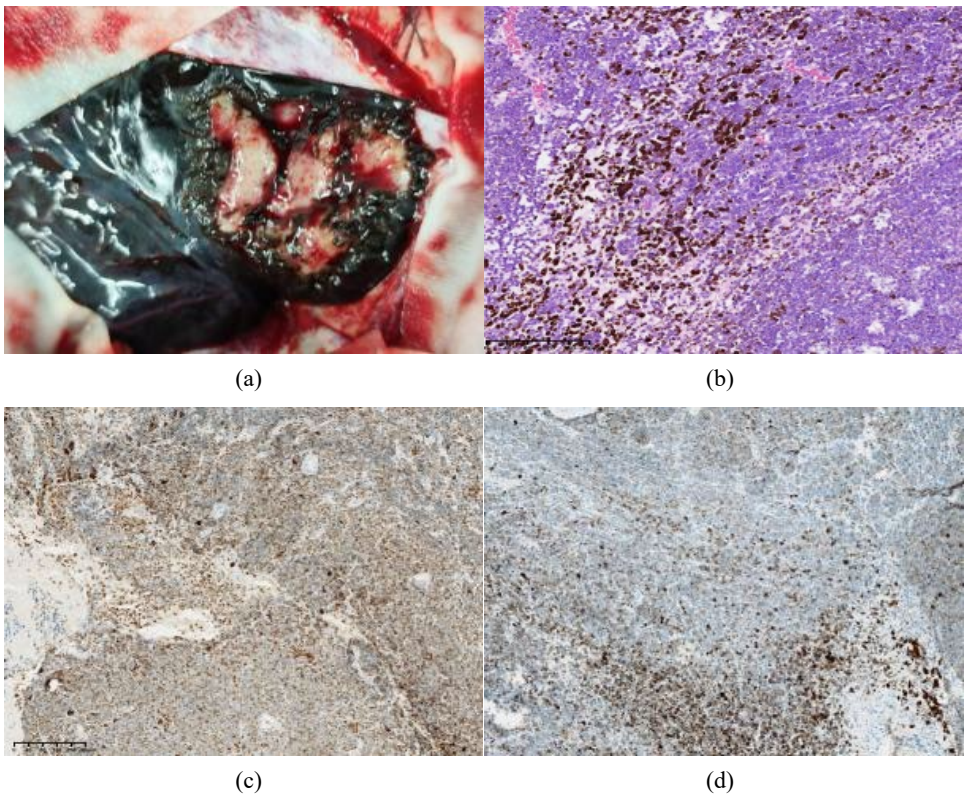
影像学检查：颅脑 MRI 平扫 +DWI 示双侧大脑半球及小脑半球异常信号，T1WI 等/稍低信号、T2WI 及 FLAIR 高信号，右侧为著；钆增强扫描示双侧脑膜弥漫性增厚并强化(图 1)。18F-FDG PET-CT 示双侧额颞叶、小脑幕区斑片状异常高代谢，符合脑膜原发肿瘤表现。

脑脊液检查：细胞学示异常异型细胞，考虑黑色素细胞瘤，脑脊液蛋白升高、葡萄糖降低。

手术及病理：行右额脑病损切除术，术中见右额颞蛛网膜下腔弥漫性黑褐色病变，厚度约 2 mm，与脑表面血管粘连，分块切除活检。病理镜下示肿瘤细胞富含黑色素，弥漫片状分布，侵犯脑实质，核分裂易见(HE × 200)。免疫组化：Ki-67 (+约 10%)、Melan-A (+)、S-100 (+)、SOX-10 (+)、Vimentin (+)、BRAF V600E (-) (图 2)。S-100 染色呈阳性反应，证实神经外胚层起源。有丝分裂活性明显，许多肿瘤细胞还有包浆内棕色颗粒色素。抗黑素体抗体免疫染色检测呈阳性，暴露于黑色素，漂白剂时呈漂白，证实肿瘤变化的黑素细胞特征。

基因检测：肿瘤组织二代测序示 NRAS Q61R 基因突变，突变频率 84.7%，未检测到 BRAF、GNAQ、GNA11 等突变及融合基因。

治疗及随访：患儿家属拒绝进一步放化疗及靶向治疗，予脱水、抗癫痫等保守治疗，术后头痛呕吐症状缓解，出院后 2 个月因神经系统进行性恶化死亡。



(a) (b)

(c) (d)

Figure 2. Diffuse black-brown lesion in the right frontotemporal cerebral subarachnoid space, without adhesion to the dura mater, with marked bleeding during dissection (a). Microscopic findings combined with immunophenotype were consistent with melanoma (b). S-100 staining was positive (c). Immunostaining for the anti-melanosome antibody Melan-A was positive (d)

图 2. 右额颞脑蛛网膜下腔弥漫性黑褐色病变，与硬膜无粘连，分离时明显渗血图 (a)。镜下表现结合免疫表型，符合黑色素瘤图 (b)。S-100 染色呈阳性反应图 (c)。抗黑素体抗体免疫染色检测呈阳性图 (d)

3. 文献回顾与讨论

3.1. 临床特征与诊断

PDLM 好发于儿童及 40 岁左右成人，儿童患者多为学龄期儿童，无明显性别差异[9]。核心临床表现为颅内高压(头痛、呕吐、乳头水肿)、癫痫发作、局灶性神经功能缺损，部分伴脊髓受累症状，与本例患儿表现一致[10]。因症状非特异性，初诊易误诊为感染性脑膜炎、淋巴瘤等，高结核流行地区需警惕与结核性脑膜炎混淆[4]。

影像学是重要筛查手段，典型 MRI 表现为弥漫性软脑膜增厚强化，T1WI 高信号、T2WI 等/低信号，与黑色素含量相关；无色素型病例可表现为 T1WI 等信号，增加诊断难度[11]。18F-FDG PET-CT 可显示病灶高代谢，但仅为辅助诊断，不能确诊[12]。

脑脊液检查可作为初筛，典型表现为蛋白升高、低糖、异常细胞学，但约 30%病例脑脊液未发现恶性细胞，不能排除诊断[5]。脑膜活检 + 免疫组化是确诊金标准，特征性免疫表型为 Melan-A (+)、S-100 (+)、SOX-10 (+)，其中 SOX-10 为高敏感特异性标志物，敏感性达 97%~100%，可鉴别其他脑膜肿瘤[13]；Ki-67 阳性率可评估肿瘤增殖活性，儿童病例多为 10%~55% [7]。

3.2. 基因诊断的核心价值

对于病理特征不典型的 PDLM，基因检测是明确诊断、分子分型的关键，可弥补病理检查的局限性。目前已明确 PDLM 存在明显的年龄相关分子特征：成人以 GNAQ、GNA11 突变为主，突变率约 60%~70%，调控细胞增殖及血管生成[6]；儿童以 NRAS Q61 突变(Q61K/R)为主，其次为 BRAF V600E 突变，NRAS 突变通过激活 RAF-MEK-ERK 通路促进肿瘤细胞增殖侵袭[7] [14]。

本例患儿检测到 NRAS Q61R 突变，突变频率 84.7%，与文献报道儿童 PDLM 突变特征一致，进一步证实基因检测对确诊的价值。此外，基因检测可指导治疗方案选择，如 NRAS 突变提示可采用 MEK 抑制剂靶向治疗，BRAF V600E 突变可选用 BRAF 抑制剂，为精准治疗提供依据[5]。

3.3. 治疗现状与靶向治疗前景

3.3.1. 传统治疗局限性

PDLM 恶性程度高，传统治疗效果极差。手术以活检明确诊断为主，无法根治性切除，仅能缓解局部压迫[8]；放疗包括颅脊髓放疗、立体定向放射外科，可暂时控制颅内病灶，但不能延长生存期，且儿童放疗远期神经毒性大[15]；化疗以替莫唑胺、顺铂为主，肿瘤细胞易产生耐药性，临床获益有限[9]。目前儿童 PDLM 主要死因为进行性神经功能障碍及颅内高压，中位生存期不足 7 个月[8]。

3.3.2. 靶向治疗研究进展

随着分子机制研究深入，靶向突变基因的精准治疗成为 PDLM 治疗的核心方向，其中 NRAS 突变相关靶向治疗最具研究价值：

1、MEK 抑制剂：NRAS 突变通过激活 MEK/ERK 通路驱动肿瘤发生，MEK 抑制剂可直接阻断该通路，抑制肿瘤增殖。个案报道显示，NRAS Q61R 突变儿童 PDLM 患者予比尼美替尼(MEK 抑制剂)联合纳武利尤单抗(免疫检查点抑制剂)治疗后，颅外转移灶显著缩小，颅内病灶稳定[14]，证实 MEK 抑制剂对儿童 NRAS 突变 PDLM 的有效性。此外，曲美替尼等 MEK 抑制剂也在黑色素瘤中显示出良好疗效，为 PDLM 治疗提供参考[5]。

2、STK19 抑制剂：研究发现 STK19 激酶是 NRAS 活性的关键调节因子，其缺失可使 NRAS 活性降低 35.1%，并抑制下游 RAF-MEK-ERK 及 PI3K-AKT 通路[16]。STK19 抑制剂可特异性抑制 NRAS 突变

肿瘤细胞生长，与 MEK 抑制剂联合使用可增强疗效，为 NRAS 突变 PDLM 提供新的联合治疗策略，目前处于临床前研究阶段。

3、BRAF 抑制剂：对于 BRAF V600E 突变 PDLM 患者，维莫非尼、达拉非尼等 BRAF 抑制剂联合 MEK 抑制剂可显著抑制肿瘤生长，在皮肤黑色素瘤中已成为标准治疗，有望推广至中枢神经系统黑色素瘤[6]。

3.3.3. 联合治疗策略

单一靶向治疗易耐药，“放疗 + 免疫 + 靶向”联合治疗是儿童 PDLM 研究方向：放疗控颅内病灶，免疫检查点抑制剂激活全身抗肿瘤免疫，MEK 抑制剂靶向驱动通路，三者协同稳定颅内病灶[14]，其安全性与有效性需大样本试验验证。

联合治疗增效与毒性存在矛盾。放疗与免疫检查点抑制剂(ICIs)理论上协同，已在 1 例 BRAF V600E 突变患儿中显效[17]，但二者联合可能加剧中枢炎症，靶向与 ICIs 联用增加免疫相关不良事件。儿童 ICIs 安全性数据匮乏[18]，伊匹单抗在儿童中不良事件出现早、反应剧烈，PDLM 患儿耐受神经毒性的安全窗口极窄[19]。

血脑屏障是主要短板。放疗对血脑屏障的破坏局限且短暂，ICIs 穿透能力有限，MEK 抑制剂脑穿透性受外排转运体限制[20]，三者药效动力学不一致，可能影响颅内病灶打击效果，需 PDLM 模型验证。

现有临床证据存在局限。Shahab 等人的个案[14]具启示性但有偏倚，McKeiver 等人的文献回顾[21]受病例数和质量限制仅为假说。儿童与成人黑色素瘤分子驱动机制不同[22]，成人治疗经验不可外推。

克服挑战需多维度推进：开发高脑穿透性靶向药[20]；开展儿童前瞻性试验；脑脊液液体活检指导治疗调整[23]；探索靶向与免疫治疗最佳序贯策略。

3.4. 鉴别诊断

PDLM 需与以下疾病鉴别：① 结核性脑膜炎：有结核接触史，脑脊液抗酸染色阳性，抗结核治疗有效；② 转移性脑膜癌病：有颅外肿瘤病史，脑脊液可找到肿瘤细胞；③ 脑膜瘤：影像学示局限性肿块，病理及免疫组化无黑色素细胞标志物表达；④ Sturge-Weber 综合征：伴面部血管痣，影像学示脑回样钙化[4] [10]。基因检测可通过突变特征进一步鉴别，如脑膜瘤无 NRAS、BRAF 等突变，转移性癌病可检测到原发肿瘤相关突变。

4. 结论

儿童原发性弥漫性软脑膜黑色素瘤病临床罕见、侵袭性强，临床表现及影像学缺乏特异性，易误诊，脑膜活检联合免疫组化是确诊基础，基因检测是明确分子分型、指导治疗的关键，NRAS Q61 突变是儿童病例的核心分子特征。传统放化疗效果有限，患儿预后极差，以 MEK 抑制剂为核心的靶向治疗为该病带来新希望，“放疗 + 免疫 +MEK 抑制剂”联合治疗有望改善患儿生存期，STK19 抑制剂等新靶点为后续研究提供方向。临床需加强对本病的认识，尽早完善病理及基因检测，及时给予个体化治疗，同时需开展多中心前瞻性临床试验，验证靶向治疗的安全性及有效性。

伦理批准

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