中枢神经系统受累的ALK阳性组织细胞增生症临床病理分析

任逸霏▲ 张美琳▲ 程园园 熊 佶 汪 寅 唐 峰 杜尊国△
(复旦大学附属华山医院病理科 上海 200040)

【摘要】 目的 总结分析累及中枢神经系统(central nervous system,CNS)的间变性淋巴瘤激酶(anaplastic lymphoma kinase,ALK)阳性组织细胞增生症(ALK-positive histiocytosis,APH)的临床病理特征、影像学表现、治疗及预后,以提高对该罕见疾病的认识。**方法** 回顾性分析复旦大学附属华山医院2019—2023年确诊的5例累及CNS的APH病例,收集其临床、影像学及病理学资料,结合免疫组织化学染色(immunohistochemistry,IHC)、荧光原位杂交(fluorescence in situ hybridization,FISH)及高通量测序等技术进行辅助诊断及分子特征探索,并对既往文献报道进行总结分析。**结果** 5例患者均为男性,平均年龄27.6岁,其中2例为全身多系统受累,3例为CNS单系统受累。影像学显示多系统患者颅内病灶多发,单系统患者颅内病灶单发,病灶边界清晰,可伴均匀强化。组织学表现为肿瘤细胞与淋巴细胞混杂分布,1例淋巴细胞与肿瘤细胞呈"明暗交替"排列,4例可见肉芽肿样改变,核沟、核切迹、核扭曲常见,肿瘤常浸润周围组织。IHC显示肿瘤表达组织细胞标记CD68/CD163,ALK表达以胞质为主。5例组织FISH检测均提示*ALK*基因重排,其中2例高通量测序提示KIF5B-ALK融合。3例单系统患者经手术切除或术后联合化疗/ALK抑制剂治疗后获得完全缓解;2例多系统型患者中,1例部分缓解,1例疾病进展。**结论** 累及CNS的APH术前易误诊,其组织学特征、ALK免疫组化表达及*ALK*基因融合具有诊断价值。单系统型患者总体预后好于多系统型(其他人群),根治性切除对单系统型患者有效,多系统型患者以全身系统性治疗为主,多学科合作对精准诊疗至关重要。

【关键词】 组织细胞增生症; 中枢神经系统(CNS); 影像学; 病理学
【中图分类号】 R44 **【文献标志码】** A **doi**:10.3969/j.issn.1672-8467.2025.06.008

Clinicopathological analysis of ALK-positive histiocytosis involving central nervous system

REN Yi-fei▲, ZHANG Mei-lin▲, CHENG Yuan-yuan, XIONG Ji, WANG Yin, TANG Feng, DU Zun-guo△
(*Department of Pathology, Huashan Hospital, Fudan University, Shanghai* 200040, *China*)

【Abstract】 Objective To summarize and analyze the clinicopathological characteristics, imaging manifestations, treatment and prognosis of anaplastic lymphoma kinase (ALK)-positive histiocytosis (APH) involving the central nervous system (CNS), so as to enhance understanding of this rare disease. **Methods** A retrospective analysis was conducted on 5 cases of CNS-involved APH diagnosed in Huashan Hospital, Fudan University between 2019 and 2023. Clinical, imaging and pathological data were collected, and supplemented by immunohistochemical staining (IHC), fluorescence in situ hybridization (FISH) and high-throughput sequencing for auxiliary diagnosis and molecular characterization. The

▲REN Yi-fei and ZHANG Mei-lin contributed equally to this work
△Corresponding author E-mail:duzunguo@fudan.edu.cn
网络首发时间:2025-10-31 14:49:49 网络首发地址:https://link.cnki.net/urlid/31.1885.R.20251030.1527.010

findings were summarized and integrated with previous literature for a comprehensive analysis. **Results** All five patients were male, with a mean age of 27.6 years, in which 2 cases exhibited multi-system involvement, while 3 cases exhibited single system involvement. Imaging revealed multiple intracranial lesions in multi-system cases and solitary lesions in single system cases, with well-defined boundaries and homogeneous enhancement. Histologically, tumor cells were intermingled with lymphocytes, displaying an alternating "light and dark" pattern in 1 case. Granuloma-like structures were observed in 4 cases, along with frequent nuclear grooves, indentations and convolutions. Tumor cells usually infiltrated surrounding tissues. IHC demonstrated that tumors expressed histiocytic markers (CD68/CD163) and ALK predominantly expressed in the cytoplasm. FISH confirmed *ALK* gene rearrangements in all patients, while high-throughput sequencing identified KIF5B-ALK fusions in 2 cases. All single system CNS cases achieved complete remission after surgical resection with or without adjuvant chemotherapy/ALK inhibitors. Among multi-system cases, one achieved partial remission, and one experienced relapse and progression. **Conclusion** CNS APH is prone to preoperative misdiagnosis. Its histopathological features, ALK immunohistochemical expression, and *ALK* gene fusions are critical for diagnosis. Patients with single system involvement demonstrate overall superior outcomes compared to multi-system cases. Total resection is effective for localized disease, while multi-system cases require systemic therapy. Multidisciplinary collaboration is crucial for precise diagnosis and treatment.

【Key words】 histiocytosis; centrals nervouss systems (CNS); radiology; pathology

间变性淋巴瘤激酶(anaplastic lymphoma kinase,ALK)阳性组织细胞增生症(ALK-positive histiocytosis,APH)是一种罕见的组织细胞肿瘤,具有特征性的ALK基因重排,第5版WHO淋巴造血组织肿瘤分类将其纳入为一类独立的组织细胞肿瘤。APH最早于2008年由Chan等[1]报道并命名,至今为止仅有60余例报道。中枢神经系统(central nervous system,CNS)是APH最常见的受累部位之一,然而现有报道尚未对累及CNS的APH病例的影像学及病理学特征、治疗方式及预后等进行系统的总结分析。现报道5例累及CNS的APH病例,并对既往报道的APH病例进行文献复习,总结分析其临床病理学特征,以提高对该罕见疾病的认识及诊疗水平。

资料和方法

资料收集 2019—2023年复旦大学附属华山医院病理科共诊断170余例组织细胞增生性病变,病种覆盖朗格汉斯组织细胞增生症(Langerhans cell histiocytosis, LCH)、Erdheim-Chester病(Erdheim-Chester disease,ECD)、Rosai-Dorfman病(Rosai-Dorfman disease,RDD)、幼年性黄色肉芽肿(juvenile xanthogranuloma,JXG)及组织细胞肉瘤,发病部位涵盖骨、甲状腺、肝、肺、皮肤、CNS、软组织及淋巴结,其中确诊APH者5例,均存在CNS受累,且具有完整的临床、影像学及病理学资料。回顾性分析5例患者的性别、年龄、临床症状、影像学表现、术前诊断、治疗方法以及病理学特征,并联合放射科、神经外科与血液科等多学科会诊,最终明确病变性质,共同参与治疗决策制定及随诊随访。本研究通过复旦大学附属华山医院伦理委员会伦理批准[批件号:(2025)临审第(1172)],并获得患者远程知情同意,同意资料匿名用于学术发表。

方法 5例患者的手术切除/活检组织均经4%甲醛水溶液固定、脱水、石蜡包埋制片及HE染色。IHC采用LEICA BOND-MAX全自动免疫组织化学仪完成(参照EnVision两步法原则),选用的一抗包括CD68、CD163、SOX10、CyclinD1(北京中杉金桥生物技术有限公司),S100、CD34、Ki67(上海长岛生物技术有限公司),CK、CD1a、GFAP、EMA、ALK(福州迈新生物技术开发有限公司)。FISH检测采用ALK位点特异性红绿分离探针(武汉康录生物技术股份有限公司),计数100个带有完整信号的细胞。BRAF V600E测序采用扩增阻滞突变系统PCR(ARMS-PCR)技术(厦门艾德生物医药科技股

份有限公司）。1例高通量测序共检测769个肿瘤相关基因，使用Qubit dsDNA HS检测试剂盒（美国Thermo Fisher Scientific公司），采用Illumina NovaSeq 6000系统进行双端测序。另1例高通量测序由上海亿康医学检验所有限公司进行，共检测600个肿瘤相关基因。

结　　果

临床资料　5例APH患者均为男性，年龄18～37岁，平均年龄27.6岁。5例患者中，3例为CNS单系统受累，CNS病灶为单发；2例为全身多系统受累，CNS病灶为多发。既往报道[2-19]的69例与本文5例APH病例的重要临床病理特征见表1。

5例患者均无特异性临床表现，但存在神经系统相关症状，包括头晕、头痛、一侧头部及颜面部麻木及疼痛、一侧肢体麻木、无力等。多系统受累患者还存在其他部位疼痛、肿胀或麻木。5例患者起病均较为缓慢，症状出现至就诊时间间隔为半个月至8个月不等。5例患者术前均未明确诊断，颅内单发患者初诊结果多考虑为脑膜瘤、CNS淋巴瘤或神经鞘瘤，全身性患者术前多考虑为淋巴瘤、多发性骨髓瘤或炎症性病变。单系统患者均接受颅内病灶切除术，术后1例联合应用ALK抑制剂靶向治疗，另有1例联合甲氨蝶呤鞘内注射化疗。多系统受累患者中1例接受了颅内病灶切除及骨病灶的部分切除，另1例颅内及肺部病灶经穿刺活检获取组织，颅内部分病灶经伽马刀治疗；2例患者后续均应用ALK抑制剂。随访至2024年3月，3例单系统受累患者均获得完全缓解（complete remission，CR），2例多系统受累患者中1例获得部分缓解（partial remission，PR），患者情况稳定，无复发及进展，另1例于ALK抑制剂停药半年后病情复发，出现新发病灶。

表1　文献及本文报道的74例ALK阳性组织细胞增生症

Tab 1　74 cases of ALK-positive histiocytosis reported in the literature and this study

Authors	Gender	Age	Orangs involved	Clinical phenotypic group	ALK staining pattern	Gene fusion	OS	Outcome
Aoki, *et al*[2]	M	3 y	Bilateral nasal/paranasal sinuses, CNS	Group 1B	Cytoplasmic	KIF5B-ALK	/	/
JABER, *et al*[3]	M	27 y	L3 level filum terminale	Group 2	/	KIF5B-ALK	9 mo	0
Syrykh, *et al*[4]	F	37 y	LN, breast, bone	Group 1B	Strong nuclear and cytoplasmic	ALK-FISH+	48 mo	0
Guo, *et al*[5]	M	18 mo	CNS	Group 2	/	KIF5B-ALK	8 mo	1
Qiu, *et al*[6]	M	49 y	CNS, LN, lung, liver, pancreas, prostate, parotid gland, pleura, bone	Group 1B	Cytoplasmic	KIF5B-ALK	5 mo	0
Tian, *et al*[7]	F	51 y	Lung, LN, CNS	Group 1B	Cytoplasmic	KIF5B-ALK	10 mo	0
Wang, *et al*[8]	M	3 y	Skin	Group 2	/	ALK-FISH+	/	/
He, *et al*[9]	M	1 y 4 mo	CNS, lung, bone	Group 1B	/	KIF5B-ALK	2 mo	1
Yuan, *et al*[10]	M	48 y	Lung	Group 2	/	ALK-FISH+	/	/
Bai, *et al*[11]	F	52 y	Lung	Group 2	/	EML4-ALK	5 mo	0
Alizadeh, *et al*[12]	M	30 y	CNS	Group 2	/	KIF5B-ALK	/	/
Liu, *et al*[13]	M	38 y	Lung, mediastinum, LN	Group 1B	Diffuse strong cytoplasmic; membranous	EML4-ALK	26 mo	0
	F	51 y	CNS, lung, LN	Group 1B	Diffuse moderate cytoplasmic; memebranous	KIF5B-ALK	24 mo	0
	M	32 y	Liver, gallbladder, skin, lung, pancreas, kidney, LN	Group 1B	Diffuse moderate cytoplasmic	VRK2-ALK, DCTN1-ALK	31 mo	0
	M	17 mo	CNS, lung, liver, skin	Group 1B	Diffuse strong cytoplasmic	KIF5B-ALK	8 mo	1
Tran, *et al*[14]	F	20 y	Mesentery	Group 2	/	TRIM33-ALK	12 mo	0
Kurita, *et al*[15]	F	38 y	Breast	Group 2	/	KIF5B-ALK	5 mo	0

(续表 1)

Authors	Gender	Age	Orangs involved	Clinical phenotypic group	ALK staining pattern	Gene fusion	OS	Outcome
Lucas, *et al*[16]	F	7 y	CNS	Group 2	/	KIF5B-ALK	12 mo	0
	F	10 y	CNS	Group 2		KIF5B-ALK	6 mo	0
Huang, *et al*[17]	M	71 y	Bladder, penis, testis, skin, LN, bone	Group 1B	/	KIF5B-ALK	30 mo	0
Chan, *et al*[1]	F	neonate	Liver, spleen, bone marrow, skin	Group 1A		TPM3-ALK	30 mo	0
	F	3 mo	Liver, spleen, bone marrow	Group 1A	Membranous and weak cytoplasmic	/	60 mo	0
	F	3 mo	Liver, spleen, bone marrow	Group 1A		/	84 mo	0
Chang, *et al*[18]	F	2 mo	Liver, spleen, bone marrow	Group 1A		KIF5B-ALK	24 mo	0
	M	3 mo	Liver, bone marrow, skin, kidney, lung	Group 1A		KIF5B-ALK	48 mo	0
	M	2 y 9 mo	Duodenum, bone marrow, CNS	Group 1A	Cytoplasmic	ALK-FISH+	2 mo	1
	M	2 y 3 mo	Skin	Group 2		KIF5B-ALK	30 mo	0
	M	15 y	CNS	Group 2		KIF5B-ALK	6 mo	0
	M	16 y	Skin/soft tissue	Group 2		COLIA2-ALK	36 mo	0
	F	40 y	Breast	Group 2		KIF5B-ALK	42 mo	0
Kemps, *et al*[19]	F	0 d	Liver, spleen, bone marrow, lung, kidney	Group 1A	Light cytoplasmic; membranous	/	42 mo	0
	F	27 d	Liver, spleen, bone marrow, kidney	Group 1A	Diffuse cytoplasmic; membranous	ALK-FISH+	84 mo	0
	M	1 mo	Liver, spleen, bone marrow, kidney, skin	Group 1A	Granular cytoplasmic with focal Golgi dot-like accentuation;no membranous	KIF5B-ALK	1 mo	1
	F	2 mo	Liver, spleen, bone marrow	Group 1A	Scant cytoplasmic; strong membranous	/	54 mo	0
	F	4 mo	Liver, bone marrow	Group 1A	Weak cytoplasmic; strong membranous	ALK-FISH+	/	/
	M	5 mo	Liver, spleen, bone marrow	Group 1A	Diffuse dark cytoplasmic (clone 5A4) to more light granularcytoplasmic (clone ALK1); membranous (both)	CLTC-ALK	48 mo	0
	F	3 mo	Bone, lung, liver	Group 1B	Diffuse cytoplasmic with Golgi dot-like accentuation; membranous	TPM3-ALK	24 mo	0
	F	9 mo	Lung, skin, kidney	Group 1B	Diffuse granular cytoplasmic with rare Golgi dot-likeaccentuation; no membranous	ALK-FISH+	24 mo	0
	M	10 mo	CNS, lung, liver, soft tissue	Group 1B	Very weak diffuse cytoplasmic; no membranous	KIF5B-ALK	13 mo	0
	F	2 y	CNS, bone, lung, liver, skin, soft tissue, LN, kidney, breast, pancreas	Group 1B	Diffuse dark cytoplasmic (clone D5F3) to more light, granular cytoplasmic with Golgi dot-like accentuation (clone ALK1); no membranous	KIF5B-ALK	21 mo	0

(续表 1)

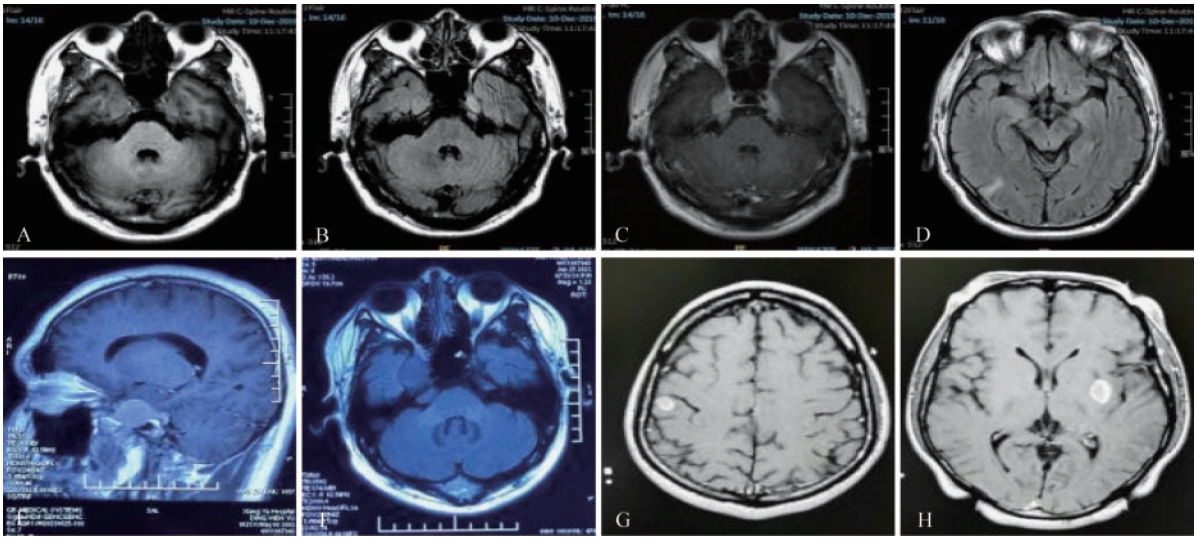
Authors	Gender	Age	Orangs involved	Clinical phenotypic group	ALK staining pattern	Gene fusion	OS	Outcome
	F	10 y	CNS, bone, lung, LN, cervix, thyroid, submandibular salivary gland	Group 1B	Diffuse cytoplasmic; no membranous	KIF5B-ALK	24 mo	0
	F	19 y	CNS/PNS, bone, lung, liver, LN, breast, pancreas	Group 1B	Golgi dot-like cytoplasmic only; no membranous	KIF5B-ALK	24 mo	0
	M	21 y	Liver, skin, colorectum	Group 1B	Very weak cytoplasmic blush to negative; no membranous	TFG-ALK	2 mo	1
	F	28 y	CNS/PNS, bone	Group 1B	Granular cytoplasmic with Golgi dot-like accentuation; nomembranous	KIF5B-ALK	9 mo	0
	M	29 y	PNS, bone	Group 1B	Diffuse cytoplasmic with Golgi dot-like accentuation; nomembranous	KIF5B-ALK	30 mo	0
	F	41 y	CNS, bone, lung, skin, soft tissue, LN	Group 1B	Granular cytoplasmic with rare Golgi dot-like accentuation;no membranous	KIF5B-ALK	72 mo	0
	F	7 mo	CNS	Group 2	Granular cytoplasmic with Golgi dot-like accentuation insome cells; no membranous	KIF5B-ALK	5 mo	0
	F	9 mo	CNS	Group 2	Diffuse cytoplasmic with Golgi dot-like accentuation; membranous	ALK-FISH+	/	/
	M	2.5 y	CNS	Group 2	Diffuse cytoplasmic; no membranous	KIF5B-ALK	16 mo	0
	F	3 y	CNS	Group 2	Focal, weak diffuse cytoplasmic with Golgi dot-likeaccentuation; no membranous	KIF5B-ALK	12 mo	0
	F	3 y	PNS	Group 2	Diffuse cytoplasmic with Golgi dot-like accentuation; nomembranous	KIF5B-ALK	30 mo	0
	F	7 y	CNS	Group 2	Diffuse granular cytoplasmic; no membranous	KIF5B-ALK	6 mo	0
	F	11 y	CNS	Group 2	Diffuse granular cytoplasmic; no membranous	KIF5B-ALK	9 mo	0
	M	11 y	PNS	Group 2	Diffuse granular cytoplasmic; no membranous	ALK-FISH+	216 mo	0
	M	12 y	PNS	Group 2	Diffuse cytoplasmic with Golgi dot-like accentuation; membranous	KIF5B-ALK	30 mo	0
	F	13 y	CNS/PNS	Group 2	Diffuse cytoplasmic with Golgi dot-like accentuation; nomembranous	KIF5B-ALK	30 mo	0
	M	20 y	PNS	Group 2	Diffuse granular cytoplasmic; no membranous	KIF5B-ALK	7 mo	0
	M	20 y	CNS	Group 2	Variable focal, weak cytoplasmic to negative; nomembranous	KIF5B-ALK	10 mo	0

(续表 1)

Authors	Gender	Age	Orangs involved	Clinical phenotypic group	ALK staining pattern	Gene fusion	OS	Outcome
	F	6 mo	Skin	Group 2	Diffuse cytoplasmic with Golgi dot-like accentuation; nomembranous	KIF5B-ALK	24 mo	0
	M	7 mo	Skin	Group 2	Diffuse granular cytoplasmic with Golgi dot-like accentuation; no membranous	KIF5B-ALK	13 mo	0
	F	21 mo	Skin	Group 2	Diffuse granular cytoplasmic; no membranous	KIF5B-ALK	24 mo	0
	M	2 y	Soft tissue	Group 2	Diffuse dark cytoplasmic; subset possibly nuclear; nomembranous (clone 5A4, lung staining protocol). Focal/Golgi dot-like cytoplasmic; no nuclear or membranous(clone 5A4, lymphoma staining protocol)	KIF5B-ALK	14 mo	0
	F	3 y	Soft tissue	Group 2	Diffuse light granular cytoplasmic with dark Golgi-dot likeaccentuation; no membranous	KIF5B-ALK	14 mo	0
	M	3 y	Soft tissue	Group 2	Golgi dot-like cytoplasmic only (focal weak); nomembranous	KIF5B-ALK	36 mo	0
	F	10 y	Skin	Group 2	Diffuse granular cytoplasmic with Golgi dot-like accentuation; no membranous	KIF5B-ALK	1 mo	0
	F	10 y	Bone	Group 2	Golgi dot-like cytoplasmic only (focal weak); nomembranous	KIF5B-ALK	60 mo	0
	M	11 y	Soft tissue	Group 2	Diffuse cytoplasmic with Golgi dot-like accentuation; membranous	KIF5B-ALK	15 mo	0
	M	17 y	Lung	Group 2	Diffuse granular cytoplasmic; membranous	EML4-ALK	/	/
	F	41 y	Bone	Group 2	Diffuse cytoplasmic with Golgi dot-like accentuation; membranous	DCTN1-ALK	24 mo	0
Ren, *et al*	M	37 y	CNS, bone, lung, pleura, pancreas, prostate, soft tissue	Group 1B	Diffuse moderate cytoplasmic; memebranous	KIF5B-ALK	51 mo	0
	M	18 y	CNS	Group 2	Diffuse strong membranous	ALK-FISH+	36 mo	0
	M	31 y	CNS	Group 2	Diffuse strong cytoplasmic; membranous	ALK-FISH+	17 mo	0
	M	21 y	CNS	Group 2	Diffuse moderate cytoplasmic; memebranous	ALK-FISH+	21 mo	0
	M	31 y	CNS, thyroid, lung, pleura, liver, spleen, prostate, stomach, bone, LN, soft tissue	Group 1B	Diffuse moderate cytoplasmic; nuclear	KIF5B-ALK	45 mo	0

CNS: Central nervous system; LN: Lymph node; PNS: Peripheral nervous system; /: Not available; 0: Survival; 1: Death.

影像学表现 5例患者均于术前接受头颅MRI检查（图1）。单系统受累患者颅内病灶为单发，其中1例位于鞍旁及斜坡，1例位于脑干，1例位于额顶叶。多系统受累患者颅内病灶为多发，1例累及海绵窦区及枕叶，1例累及基底节、顶叶及鞍旁。5例患者头颅MRI均表现为颅内占位性病变，可呈团块状、类圆形或小结节状，病变边界较清，可出现轻度占位效应，表现为周围脑组织水肿。2例患者MRI增强序列显示病变均匀强化。2例多系统受累患者接受全身PET/CT检查，显示多器官多发结节状影伴放射性摄取异常增高。



A-C：(case 1) Axial images of MRI scans of the head, showing irregular mass in the bilateral cavernous sinus of equal T1-Flair signal and increased T2-Flair signal, T1-Flair contrast-enhanced MRI showed homogenous enhancement, with clear boundaries and thickening and enhancing of adjacent bilateral trigeminal nerves；D：(case 1) T2-Flair MRI showed a focus of high signal in the right occipital cortex；E-F：(case 4) Axial and sagittal MRI showed a mass of T1-Flair hyperintensity and T2-Flair isointensity in the right parasellar and clivus, with clear boundaries；G-H：(case 5) T1-weighted contrast-enhancement showed circular enhanced nodules in the right parietal lobe and the left basal ganglia, with clear boundaries.

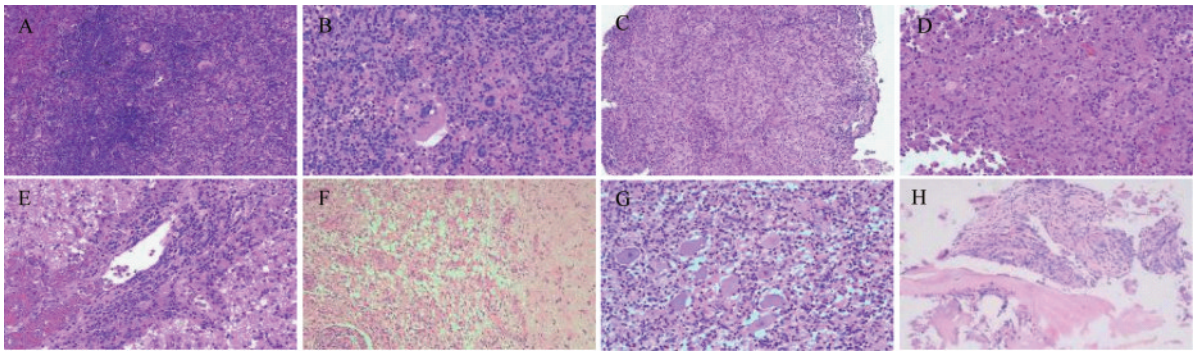
图1 累及CNS的APH患者的头颅MRI图像

Fig 1 Cranial MRI images of patients with APH involving CNS

组织学特征 5例患者CNS病灶的活检/切除组织均经充分取材及显微镜下评估（图2）。5例CNS病变低倍镜下最为显著的特点是肿瘤细胞与较为丰富的淋巴细胞混杂分布，淋巴细胞可出现灶性聚集，其中1例淋巴细胞与肿瘤细胞呈“明暗交替”排列，类似于Rosai-Dorfman病的表现。肿瘤细胞排列方式可呈弥漫片状、编织状或局部漩涡状。5例CNS病变中有4例局部形成肉芽肿样结构。肿瘤浸润周围脑实质、神经、神经节及血管壁等正常组织。高倍镜下，肿瘤胞质丰富、淡粉色，可呈泡沫细胞样。细胞核圆形、卵圆形至梭形不等，核膜不规则，常出现核沟、核切迹、核扭曲等特征性改变。肾形核及马蹄形核多见。细胞核大小中等，约为静止期淋巴细胞的1.5～3倍。核染色质较细腻，可见较大的泡状核细胞，此类细胞中常见嗜酸性或嗜碱性小核仁，其余肿瘤细胞核仁不明显。10个高倍视野核分裂象计数0～12个。

免疫组化结果 5例肿瘤细胞CD68和/或CD163弥漫胞质强阳性（5/5）。在ALK表达模式方面，最常见的阳性表达模式为胞质弥漫中等-强着色（3/5，60%），1例表现为胞质弥漫中等强度着色伴部分细胞核着色（1/5），1例表现为胞膜弥漫强着色（1/5）。S-100弥漫阳性者2例（2/5），部分阳性者2例（2/5），阴性者1例（1/5）。5例中3例进行CyclinD1免疫组化染色，结果均为阳性（3/3）。CK、CD1a、GFAP、EMA、SOX-10均阴性，Ki67增殖指数为3%～20%，与核分裂象多少相关（图3）。

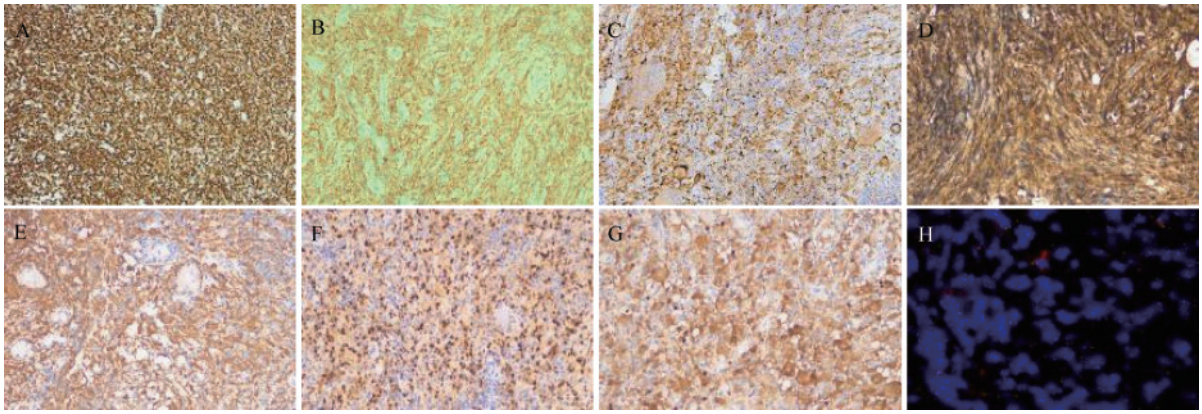
分子检测结果 5例患者ALK FISH检测结果均显示红绿信号分离，提示ALK基因易位阳性（5/5）。4例患者行BRAF V600E测序，结果显示BRAF V600E均为野生型（4/4）。2例患者进行高通量测序，结果显示发生KIF5B-ALK基因融合突变。



A: Mixed distribution of lymphocytes and tumor cells in an alternating pattern of light and dark (100×); B: Multinuclear giant cells and emperipolesis (200×); C: Granulomatoid changes were observed (40×); D: Some of the lesional cells were foamy cells (200×); E: Lymphocyte aggregation around blood vessels formed lymphocyte sheath structure (200×); F: The tumor cells infiltrated the peripheral brain parenchyma (40×); G: The tumor cells invaded the nerve roots of the cavernous sinus (200×); H: The tumor cells invaded bone tissue (200×).

图2 ALK阳性组织细胞增生症显微镜下病理形态(HE染色)

Fig 2 Pathological morphology of ALK-positive histiocytosis (HE staining)



A: ALK staining of cells with oval-shaped nuclei was diffusely cytoplasmic positive (100×); B: ALK staining of cells with short fusiform nuclei was diffusely cytoplasmic positive (100×); C: ALK staining of multinucleated giant cells was cytoplasmic positive (200×); D: CD68 staining was diffusely cytoplasmic positive (200×); E: CD163 staining was diffusely cytoplasmic positive (200×); F: CyclinD1 staining could be nuclear positive (200×); G: S-100 could be diffusely cytoplasmic and a few nuclear positive (200×); H: Fluorescence in situ hybridization ALK red-green separation probe showed intracellular red-green separation signal (1 000×).

图3 ALK阳性组织细胞增生症IHC和FISH检测结果

Fig 3 Results of immunohistochemical staining and FISH detection of ALK-positive histiocytosis

讨 论

APH是一种以ALK基因重排为特征的罕见组织细胞肿瘤,2008年该疾病首次由Chan等[1]报道,2022年Kemps等[19]的回顾性研究根据病变范围将该疾病分为3种临床类型,分别为累及肝及造血系统的多系统型(Group 1A)、其他人群的多系统型(Group 1B)及单系统型(Group 2)。第五版WHO淋巴造血系统肿瘤分类标准基本沿用该分型方法[20]。Group 1A见于0~5个月大的婴儿,多广泛累及肝、脾及骨髓,临床表现为肝脾肿大、贫血及血小板减少,还可出现白细胞增多症、肝功能异常等。多系统型(Group 1B)发病年龄较广,但平均发病年龄较轻,可有全身各器官受累,但不具备多系统型(Group 1A)的典型临床特点。单系统型同样可见于各年龄阶段,平均发病年龄较轻。多系统型(Group 1B)和单系统型(Group 2)的临床表现多依发病部位而定,表现为因占位效应或肿瘤压迫导致的疼痛、麻木或功能障碍,也可无任何症状。

根据文献报道,APH组织学表现多样,镜下类似炎症性病变。病变通常边界欠清,肿瘤细胞呈片状、编织状或漩涡状排列。肿瘤细胞具有丰富的嗜酸性至苍白的胞质,总体核质比低,细胞核可呈圆

形、卵圆形、梭形或不规则，可见较为特征性的核切迹、核沟、扭曲或分叶状核。核染色质细腻，可见小核仁。部分肿瘤细胞呈异物多核巨细胞、Touton巨细胞和泡沫细胞样，可观察到组织细胞吞噬淋巴细胞的“伸入现象”。背景中常有淋巴细胞及浆细胞浸润，还可见到中性粒细胞或嗜酸性粒细胞。本文报道的5例APH患者的CNS病灶镜下表现与既往病例报道相符，且具有一些特征性的表现，如肿瘤背景中淋巴细胞丰富，1例表现为RDD样的“明暗交替”形态，明区为肿瘤细胞，暗区为淋巴浆细胞。此外，有4例局部观察到肉芽肿样结构。既往文献关于CNS病灶的组织学描述不甚详细，有部分病例提出背景中存在密集的淋巴细胞浸润，肉芽肿样结构未被提及，因此以上特征是否为CNS病变所特有，仍需更多病例进行详细的形态学描述和总结。

IHC显示肿瘤表达组织细胞标记，如CD68、CD163、CD4、CD14和溶菌酶。Kemps等[19]提出诊断APH需至少2个组织细胞标记物阳性。ALK免疫组化阳性是诊断APH的必要条件，据既往文献报道（表1），ALK着色主要位于胞质，其次为胞质及胞膜着色，胞质及核着色者仅3例。胞质着色模式多变，范围可呈弥漫或局灶不等，着色强度弱、中等至强不等，可出现高尔基体点状（Golgi dot-like）阳性或着色增强。部分病例可出现S100和CyclinD1阳性。Ki67增殖指数总体较低，多小于10%，少数病例在20%～30%。肿瘤细胞不表达CK、CD1a、langerin、BRAF V600E等免疫组化标记。

超过80%的APH存在*KIF5B-ALK*基因融合，断裂位点主要位于*KIF5B*基因的24号外显子和ALK基因的20号外显子。本研究中2例行高通量测序，同样显示KIF5B-ALK融合。除KIF5B-ALK外，过去曾被报道[1-19]过的融合基因类型还包括*EML4-ALK*、*TPM3-ALK*、*DCTN1-ALK*、*TRIM33-ALK*、*VRK2-ALK*、*COLIA2-ALK*、*CLTC-ALK*及*TFG-ALK*。3例*EML4-ALK*融合患者均以肺部受累为主，2例*TPM3-ALK*融合患者均为累及肝及造血系统的多系统型，CNS受累患者既往报道的融合类型均为*KIF5B-ALK*。尽管融合类型是否与APH的发病部位及其他临床病理学特征相关仍待进一步研究，但这可能提示病理医师：当出现特定的融合类型时，应重点关注相关部位有无病灶（如肺、CNS）。对于多系统型，不同部位病变的融合类型是否相同仍待更多病例证实。Liu等[13]曾报道1例累及肝、胰腺、肾脏、肺、皮肤等全身多系统的病例，该病例肝脏病变样本检测出*VRK2-ALK*及*DCTN1-ALK*融合，提示同一病灶可能同时出现两种或以上融合基因类型。

需要与APH鉴别的疾病主要有LCH、JXG、ECD、RDD、上皮样纤维组织细胞瘤（epithelioid fibrous histiocytoma，EFH）、炎性肌纤维母细胞瘤（inflammatory myofibroblastic tumor，IMT）。临床工作中需结合患者年龄、发病部位、IHC及基因检测等综合判断。

根据既往病例报道提供的生存信息[1-20]，绘制APH患者生存曲线（图4），显示单系统患者（Group 2）总体预后优于多系统型（Group 1A、Group 1B），但差异不显著（P=0.08）。目前尚缺乏具有循证医学证据的指南指导APH的治疗。对于单系统型患者，根治性手术切除仍是首选的治疗策略。对于累及肝及造血系统的多系统型患者，Chan等[1]和Kemps等[19]等曾报道2例未经任何特异性治疗而自发缓解的患者。目前该类患者采用的治疗方法主要有化疗、激素治疗、静脉注射免疫球蛋白和支持治疗等。对多系统型（Group 1B）患者而言，根治性手术切除常因病变广泛难以进行，因此目前多以全身性化疗和（或）ALK抑制剂治疗为主，辅以局部手术切除。常用的化疗药物包括长春花碱、甲氨蝶呤、依托泊苷等药物联合激素（强的松或地塞米松）。

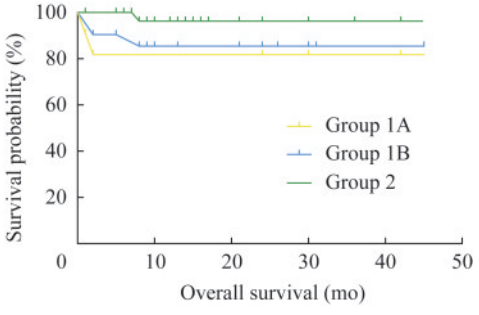


图4 3组ALK阳性组织细胞增生症患者生存曲线

Fig 4 Kaplan-Meier survival curves of 3 groups of patients of ALK-positive histiocytosis

综上所述，CNS APH在术前诊断方面存在困难且误诊率较高。CNS APH镜下呈现肿瘤细胞与较为丰富的淋巴细胞混杂分布的特点，甚至可出现RDD样的“明带”“暗带”交替形态，还可见肉芽肿样结构形成，肿瘤浸润周围正常组织。APH的治疗及

预后与其临床分型密切相关,因此结合患者的病史、影像学资料及全身PET/CT检查,并进行多学科会诊,以明确患者疾病分型尤为重要。APH作为一类罕见肿瘤,仍需要更多的病例研究对不同分型APH的预后及治疗策略提供科学、专业的指导,以期逐步提高认识,更好地实现精准诊断、风险评估和有效治疗。

作者贡献声明 任逸霏 资料收集,论文撰写。张美琳 切片制作和染色。程园园,熊佶 病例诊断和收集。唐峰,汪寅 论文修订。杜尊国 论文构思和指导。

利益冲突声明 所有作者均声明不存在利益冲突。

参 考 文 献

[1] CHAN JK, LAMANT L, ALGAR E, *et al*. ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy[J]. *Blood*, 2008, 112(7): 2965-2968.

[2] AOKI Y, MAEDA M, KISHI S, *et al*. Central nervous system involvement of systemic ALK-positive histiocytosis with KIF5B-ALK fusion[J]. *Radiol Case Rep*, 2022, 17(10): 3867-3870.

[3] JABER OI, JARRAH DA, HIASAT M, *et al*. ALK-positive histiocytosis: a case report and literature review[J]. *Turk Patoloji Derg*, 2021, 37(2): 172-177.

[4] SYRYKH C, YSEBAERT L, PéRICART S, *et al*. ALK-positive histiocytosis associated with chronic lymphocytic leukaemia/small lymphocytic lymphoma: a multitarget response under ibrutinib[J]. *Virchows Arch*, 2021, 478(4): 779-783.

[5] GUO Y, QU HB, NING G, *et al*. Case report: ALK-positive histiocytosis with KIF5B-ALK fusion in cerebrum-disseminated lesions in a child[J]. *Front Oncol*, 2022, 12(858): 939-946.

[6] QIU L, WEITZMAN SP, NASTOUPIL LJ, *et al*. Disseminated ALK-positive histiocytosis with KIF5B-ALK fusion in an adult[J]. *Leuk Lymphoma*, 2021, 62(5): 1234-1238.

[7] TIAN Y, LI J, LIU B, *et al*. ALK-positive histiocytosis with disseminated disease responded to alectinib: a case report[J]. *Ann Palliat Med*, 2021, 10(9): 10095-10101.

[8] WANG SH, HUANG HY, MEDEIROS LJ, *et al*. ALK-positive histiocytosis of external auditory canal in a 3-year-old boy[J]. *Am J Hematol*, 2024, 99(4): 739-740.

[9] HE Q, ZHANG W, LI Q. Failure of crizotinib based systemic treatment in ALK positive histiocytosis involving the central nervous system: a case report and literature review[J]. *BMC Pediatr*, 2022, 22(1): 308-315.

[10] YUAN CT, CHEN JS, HUANG YL, *et al*. ALK-positive histiocytosis presenting as a solitary pulmonary nodule[J]. *Br J Haematol*, 2022, 199(1): 7-7.

[11] BAI Y, SUN W, NIU D, *et al*. Localized ALK-positive histiocytosis in a Chinese woman: report of a case in the lung with a novel EML4-ALK rearrangement [J]. *Virchows Arch*, 2021, 479(6): 1079-1083.

[12] ALIZADEH M, RAVINDRAN A, CHKHEIDZE R, *et al*. ALK-positive histiocytosis involving the cavernous sinus: a deceptive radiologic mimic of meningioma[J]. *Radiol Case Rep*, 2023, 18(6): 2259-2263.

[13] LIU W, LIU HJ, WANG WY, *et al*. Multisystem ALK-positive histiocytosis: a multi-case study and literature review[J]. *Orphanet J Rare Dis*, 2023, 18(1): 53-64.

[14] TRAN TAN, CHANG KTE, KUICK CH, *et al*. Local ALK-positive histiocytosis with unusual morphology and novel TRIM33-ALK gene fusion[J]. *Int J Surg Pathol*, 2021, 29(5): 543-549.

[15] KURITA A, YOSHIDA M, MURATA T, *et al*. A case of ALK-positive histiocytosis with multiple lesions in the unilateral breast: a case report[J]. *Int J Surg Case Rep*, 2022, 97(107): 435-439.

[16] LUCAS CG, GILANI A, SOLOMON DA, *et al*. ALK-positive histiocytosis with KIF5B-ALK fusion in the central nervous system[J]. *Acta Neuropathol*, 2019, 138(2): 335-337.

[17] 黄海建,陈小岩. 间变性淋巴瘤激酶阳性组织细胞增生症呈系统性表现1例[J]. 中华病理学杂志, 2023, 52(7): 742-744.

[18] CHANG KTE, TAY AZE, KUICK CH, *et al*. ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion[J]. *Mod Pathol*, 2019, 32(5): 598-608.

[19] KEMPS PG, PICARSIC J, DURHAM BH, *et al*. ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition[J]. *Blood*, 2022, 139(2): 256-280.

[20] KHOURY JD, SOLARY E, ABLA O, *et al*. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms[J]. *Leukemia*, 2022, 36(7): 1703-1719.

(收稿日期:2024-03-26; 编辑:王蔚)