·代谢性肌病临床研究·

# 核黄素反应性脂质沉积性肌病临床特征与基因突变分析:两家系三例报告并文献复习

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【摘要】 **目的** 分析核黄素反应性脂质沉积性肌病临床特征和基因型,以实现早期诊断与治疗。**方法与结果** 两家系3例核黄素反应性脂质沉积性肌病患者主要表现为进行性呼吸肌、四肢近端肌无力,肌电图呈肌源性损害,油红O染色肌纤维内可见脂肪滴沉积。3例患者均存在电子转移黄素蛋白脱氢酶(*ETFDH*)基因突变,分别为c.250G > A(Ala84Thr)纯合突变和c.250G > A(Ala84Thr)、c.524G > A(Arg175His)复合杂合突变。维生素$B_2$治疗后症状明显改善,1例治疗10个月后呼吸肌和四肢近端肌无力症状完全消失,恢复正常运动功能;1例治疗2个月后行走、跑步如常,颈部肌肉恢复至正常状态;1例治疗2个月后可参加剧烈运动且无疲劳感。**结论** 核黄素反应性脂质沉积性肌病虽然以四肢近端和躯干肌无力,以及运动不耐受为主要表现,但也需注意少数以呼吸肌无力为首发症状的病例,避免漏诊和误诊。维生素$B_2$单药治疗效果极佳,症状可明显好转或痊愈。因此,临床疑似核黄素反应性脂质沉积性肌病患者可尝试维生素$B_2$诊断性治疗。

【关键词】 脂质贮积病; 电子转移黄素蛋白质类; 基因; 突变

## Clinical characteristics and gene mutation analysis of riboflavin - responsive lipid storage myopathy: report of 3 cases in 2 families and review of literature

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【**Abstract**】 **Objective** The clinical manifestation and electron transfer flavoprotein dehydrogenase

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(*ETFDH*) gene mutation of riboflavin-responsive lipid storage myopathy were analyzed for early diagnosis and treatment. **Methods** Clinical material, *ETFDH* gene mutation and the motor function before and after vitamin $B_2$ treatment in 3 patients from 2 predigrees were collected from August 2012 to March 2013 in our hospital. **Results** Case 1 was 16-year-old female. The chief complaint was difficulty of breathing and expectorating for over 3 years. Clinical symptoms included progressive respiratory muscle and proximal limb muscle weakness and worsen by fever, cardiac involvement, myopathic electromyography (EMG) changes and deposition of lipid droplets in muscle fiber by oil red O staining. Case 2 and Case 3 were brothers, the chief complaint of whom was fatigue after exercise for more than 1 year and 1 month, respectively. Clinical symptoms included significantly weakness of lower limbs and neck muscles after exercise and myopathic EMG changes. All 3 patients from two predigrees presented *ETFDH* gene mutation [c.250G > A (Ala84Thr) homozygous mutations and c.250G > A (Ala84Thr) and c.524G > A (Arg175His) compound heterozygous mutations, respectively]. They all had a dramatic response to vitamin $B_2$ treatment with muscle strength and motor function recovering to normal. The symptoms of Case 1 were completely disappeared with vitamin $B_2$ treatment for over 10 months, including respiratory muscle and proximal limb muscle weakness, and the motor function of her limbs returned to normal, characterized by completing over 10 squat-stand in 1 min. Case 2 could walk and run as ordinary people, raise his head without difficulty and play basketball about 2 h without fatigue after vitamin $B_2$ treatment for over 2 months. Case 3 could participate in any kind of strenuous exercise without fatigue after vitamin $B_2$ treatment for over 2 months. **Conclusions** Riboflavin-responsive lipid storage myopathy is mainly characterized by proximal limb and trunk muscle weakness and intolerance of movement, however, rare cases with first symptom of respiratory muscle weakness should also be concerned. In addition, it is a treatable genetic disease. The patients could be cured or significantly improved with vitamin $B_2$ monotherapy. So vitamin $B_2$ exploratory treatment should be given when the patients are suspected of riboflavin-responsive lipid storage myopathy.

**【Key words】** Lipidoses; Electron-transferring flavoproteins; Genes; Mutation

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核黄素反应性脂质沉积性肌病是一种常染色体隐性遗传性脂肪酸代谢障碍性肌病。由于该病主要由电子转移黄素蛋白(*ETF*)和电子转移黄素蛋白脱氢酶(*ETFDH*)基因突变引起的线粒体呼吸链多种脱氢酶功能障碍,使其脱氢产生的电子不能传递,导致脂肪酸、支链氨基酸、维生素B和能量代谢障碍,故又称核黄素反应性多种酰基辅酶A脱氢酶缺乏症(MADD);由于尿液气相质谱检测可检出大量戊二酸、异戊酰甘氨酸、乙基丙二酸,以及己二酸、辛二酸、癸二酸等二羧酸,故又称为核黄素反应性戊二酸血症Ⅱ型[1-2]。自1981年Carroll等[3]首先报告1例对核黄素治疗有效的核黄素反应性脂质沉积性肌病病例以来,国内外相继有多篇文献报道,临床主要表现为进展性或波动性近端型肌病、运动不耐受和颈肌无力[4-9],仅有少数文献报道为呼吸困难和心功能损害的病例[10-11]。中山大学附属第一医院神经科2012年8月-2013年3月明确诊断1例以呼吸肌受累为主诉并心脏功能损害患者,以及2例表现为波动性近端型肌病、运动不耐受和颈肌无力患者,回顾3例患者的临床诊断与治疗经过,以期提高对该病的认识和鉴别诊断能力。

## 典型病例

**例1** 女性,16岁。因呼吸困难、咳痰费力3年余,于2012年8月27日至我院就诊。患者3年前无明显诱因出现呼吸困难、咳痰费力,运动功能渐进性下降,无法正常上体育课,期间病情平稳,无明显进展。1个月前因高热(39 ℃)而使症状加重,出现四肢近端无力,上楼和双上肢上举困难,因呼吸困难于外院行气管插管呼吸机辅助通气,以及相关对症支持治疗后病情稳定。于2012年8月27日由家属用轮椅推至我院,望诊呈消瘦面容,呼吸困难、咳痰费力,发声无力。体格检查:生命体征平稳,消瘦,体重仅30 kg,神志清楚,精神差。脑神经检查无

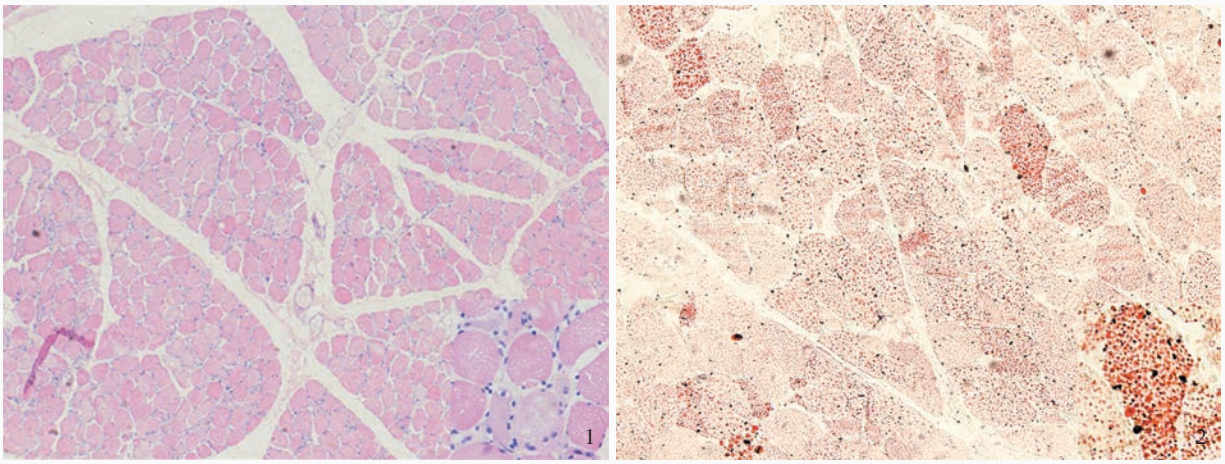

**图1** 光学显微镜观察显示，肌纤维大小明显不一致，部分肌纤维萎缩、变性、坏死，可见小灶性再生肌纤维，间质轻度增生 HE染色 ×100 **图2** 光学显微镜观察，肌纤维内可见大量脂肪滴 油红O染色 ×200

**Figure 1** Optical microscopy showed muscle fibers were not in uniform size, part with atrophy, degeneration and necrosis. Focally regenerative muscle fibers could also be seen, with hyperplasia of mesenchyme. HE staining ×100 **Figure 2** Optical microscopy showed a large number of droplets in muscle fibers. Oil red O staining ×200

异常。四肢近端肌力4级，四肢和躯干肌萎缩，肌张力降低，四肢腱反射减弱，病理征未引出。感觉系统检查无异常发现。实验室检查：发热时血清肌酸激酶（CK）955 U/L（25～200 U/L）、体温正常时28～107 U/L。心电图呈窦性心律不齐，短P-R间期，偶发房性期前收缩。胸部X线和CT检查提示心脏扩大。超声心动图显示二尖瓣前叶脱垂并轻微关闭不全，轻至中度三尖瓣关闭不全。肌电图呈肌源性损害。肌肉组织活检，肌纤维大小明显不一致，部分肌纤维萎缩、变性、坏死，可见小灶性再生肌纤维，间质轻度增生（图1）。油红O染色，肌纤维内可见较多脂肪滴（图2）。基因突变分析，存在*ETFDH*基因c.250G > A（Ala84Thr）纯合突变，其父母呈*ETFDH*基因c.250G > A（Ala84Thr）杂合突变（图3）。临床诊断：核黄素反应性脂质沉积性肌病。予维生素$B_2$ 20 mg（3次/d）口服，治疗1周后四肢肌力明显增强，脱离轮椅，可自行蹲起，深呼吸和咳痰有力，发声有力；2周后可与其父做对抗动作，遂将维生素$B_2$剂量增至25 mg（3次/d）口服；4周后肌萎缩程度明显改善、体重增加约1.50 kg；3个月后可自行上楼，蹲起速度明显加快；10个月后肌无力症状完全消失，四肢活动恢复正常，1 min内可做10个以上蹲起动作。2013年10月复查血清肌酸激酶水平为107 U/L。目前仍在随访中。

**例2** 男性，15岁。主诉运动后疲劳1年余，于2013年3月15日至我院门诊就诊。患者1年前无明显诱因出现运动后疲劳，跑步或走路300 m即感疲劳无力，休息3 min后可跑步或行走约300 m；以颈部肌无力显著，严重时不能抬头，外院两次检测血清肌酸激酶分别为500和1000 U/L。为求进一步诊断与治疗至我院就诊。体格检查：生命体征平稳，神志清楚；脑神经检查未见明显异常；四肢近端肌力5级，病理征未引出；感觉系统未见异常。实验室检查：血清肌酸激酶500～1000 U/L。心电图、超声心动图均无异常发现。肌电图呈肌源性损害。基因突变分析显示，存在*ETFDH*基因c.250G > A（Ala84Thr）和c.524G > A（Arg175His）复合杂合突变；其父母分别表现为*ETFDH*基因c.524G > A（Arg175His）和c.250G > A（Ala84Thr）杂合突变（图4）。临床诊断：核黄素反应性脂质沉积性肌病。予维生素$B_2$ 30 mg（3次/d）口服，治疗1周后跑步、行走如常，运动后（如打篮球）无明显疲劳感，抬头有力；2个月后运动（如打篮球）约2 h无疲劳感，血清肌酸激酶降至151 U/L。目前仍定期随访。

**例3** 男性，14岁，系例2胞弟，于2013年3月15日至我院门诊就诊，其主诉和症状与其胞兄类似。患者1个月前无明显诱因出现运动后肌无力，不能跑步，休息后明显好转；以双下肢和颈部肌无力明显；外院两次检测血清肌酸激酶分别为918和1366 U/L。我院体格检查：生命体征平稳，神志清楚；脑神经检查无明显异常；四肢近端肌力5级，病理征未引出；感觉系统未见明显异常。基因型同其

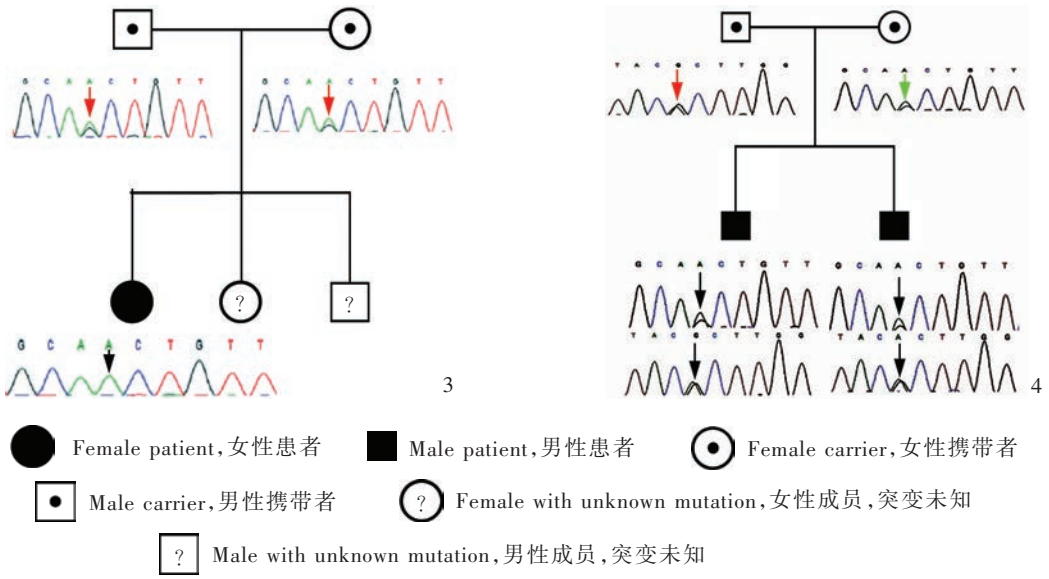


**图3**　例1家系图及基因突变分析，存在*ETFDH*基因c.250G > A（Ala84Thr）纯合突变（黑箭头所示），其父母存在*ETFDH*基因c.250G > A（Ala84Thr）突变（红箭头所示）　**图4**　例2和例3家系图及基因突变分析，存在*ETFDH*基因c.250G > A（Ala84Thr）和c.524G > A（Arg175His）复合杂合突变（黑箭头所示），其父存在*ETFDH*基因c.524G > A（Arg175His）杂合突变（红箭头所示），其母存在*ETFDH*基因c.250G > A（Ala84Thr）杂合突变（绿箭头所示）

**Figure 3**　The genogram of Case 1 presented *ETFDH* c.250G > A (Ala84Thr) homozygous mutations (black arrow indicates) and her parents presented *ETFDH* c.250G > A (Ala84Thr) mutations (red arrows indicate). **Figure 4**　The genogram of Case 2 and Case 3 showed both of them carried *ETFDH* c.250G > A (Ala84Thr) and c.524G > A (Arg175His) compound heterozygous mutations (black arrows indicate). Their father existed *ETFDH* c.524 > A (Arg175His) heterozygous mutation (red arrow indicates), and their mother carried *ETFDH* c.250G > A (Ala84Thr) heterozygous mutation (green arrow indicates).

胞兄。临床诊断：核黄素反应性脂质沉积性肌病。予维生素$B_2$ 30 mg（3次/d）口服，治疗1周后症状缓解，可短距离（约100 m）跑步，行走有力；2周后双侧小腿无力感消失，颈部肌力恢复、抬头无障碍，长时间行走无乏力感，可跑步约600 m；2个月后肌力完全恢复正常，临床症状与体征消失，可参加任何剧烈运动，血清肌酸激酶水平恢复至228 U/L。目前仍在随访中。

## 讨　论

核黄素反应性脂质沉积性肌病是一种可治性常染色体隐性遗传性脂肪酸代谢障碍性肌病，主要由*ETF*和*ETTDH*基因突变所致[12]。在正常状态下，ETF蛋白α亚基与β亚基共同组成二聚体，位于线粒体基质内，接受脂肪酸β氧化过程中多种脱氢酶脱氢产生的电子，传递至位于线粒体内膜的ETFDH蛋白，经其结合的泛醌传递至呼吸链复合体Ⅲ，生成ATP为机体提供能量[1,13]。当编码ETF蛋白α亚基的*ETFA*基因、编码β亚基的*ETFB*基因及*ETFDH*基因中任意一种发生突变均可致病[4,6]。然而，Olsen等[8]对11例核黄素反应性脂质沉积性肌病患者进行基因学检测，发现至少携带1种*ETFDH*基因突变。Wen等[7]对我国19例核黄素反应性脂质沉积性肌病患者中的18例进行基因学检测，发现至少携带1种*ETFDH*基因突变。Wang等[11]对我国53例核黄素反应性脂质沉积性肌病患者进行基因学检测，均携带*ETFDH*基因突变。因此，对于临床疑诊为核黄素反应性脂质沉积性肌病患者，应先行*ETFDH*基因突变分析，而国内两个独立小组的研究结果显示，南方人主要携带*ETFDH*基因c.250G > A（Ala84Thr）突变，北方人主要携带*ETFDH*基因c.770 A > G（Tyr257Cys）和c.1227A > C（p.L409F）突变[4,11]。本组3例来自广东省的患者均携带*ETFDH*基因c.250G > A（Ala84Thr）突变，进一步证实核黄素反应性脂质沉积性肌病主要由*ETFDH*基因突变所致，以及中国南方人*ETFDH*基因突变特点[9,11,14-15]。两家系3例患者均系父母遗传，也进一步证实Wang等[11]所阐述的中国南方人*ETFDH*基因c.250G > A（Ala84Thr）突变存在先证者效应的理论。

本组3例患者均携带*ETFDH*基因c.250G > A（Ala84Thr）突变，例1临床表现为呼吸肌和心脏功能损害，且以呼吸肌受累症状更为突出；而例2和例

3仅呈典型的波动性四肢和躯干无力，以及运动不耐受，其中例2心电图和超声心电图均无异常。相同的基因型却表现出不同的临床症状与体征，进一步说明核黄素反应性脂质沉积性肌病是一种高度异质性疾病。本组3例患者发病年龄均为青少年期，符合文献报道的*ETFDH*基因c.250G > A（Ala84Thr）和c.524G > A（Arg175His）突变与晚发型核黄素反应性脂质沉积性肌病相关的理论[9,14-15]。本组例1于发热后病情快速进展、血清肌酸激酶水平明显升高，可以解释Olsen等[13]应用患者皮肤纤维母细胞观察到的温度升高残余酶活性降低、温度降低残余酶活性升高的现象。此外，例1以呼吸困难、咳痰费力等呼吸肌受累表现为首发症状，尚属首次文献报道，尽管有少量携带*ETFDH*基因c.250G > A（Ala84Thr）突变的患者可能出现呼吸肌受累表现[10-11]，但均出现在四肢或躯干无力症状后，环境及其他因素是否影响该病的临床表现尚待进一步研究。

本组3例患者对小剂量维生素$B_2$的治疗效果极佳，病情呈“戏剧性”改善，经治疗运动功能基本恢复正常。这一结果符合我国多篇文献报道的中国人群对维生素$B_2$的敏感性高于其他种族人群[7,11]。针对*ETFDH*基因c.524G > A（Arg175His）突变，我们的研究结果符合Wang等[11]所阐述的国人对维生素$B_2$治疗敏感，不同于Yotsumoto等[10]所报告的维生素$B_2$治疗无效。相同基因型出现不同的治疗反应，说明环境及其他因素可能也参与该病对维生素$B_2$治疗的反应。

总之，核黄素反应性脂质沉积性肌病是一种可治疗的遗传代谢性疾病，*ETFDH*基因是其主要致病基因，中国南方人群主要表现为c.250G > A（Ala84Thr）突变。临床上以四肢近端和躯干肌无力，以及运动不耐受为主要表现，但需注意少数病例可以呼吸肌无力为首发症状，通过*ETFDH*基因突变分析可避免漏诊或误诊。患者对维生素$B_2$单药治疗有效，临床症状与体征可迅速好转或痊愈。因此，对于疑似核黄素反应性脂质沉积性肌病患者，可尝试进行维生素$B_2$诊断性治疗。

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·临床医学图像·

# Rosai-Dorfman病

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## Rosai-Dorfman disease

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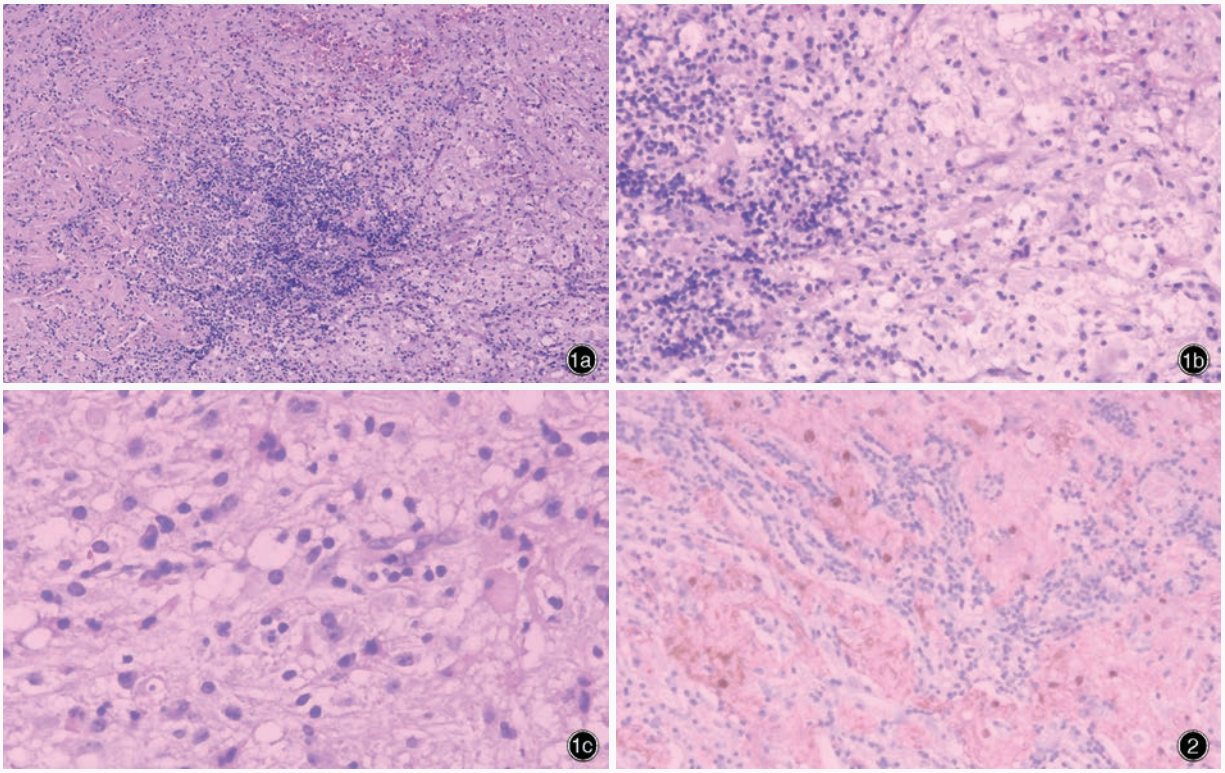


**图1** 光学显微镜观察所见 HE染色 1a 病变呈结节状，伴炎性浸润 低倍放大 1b 在淋巴细胞和浆细胞浸润中可见组织细胞散在或灶性聚集 低倍放大 1c 组织细胞胞质内可见淋巴细胞和浆细胞为其典型组织学特征 中倍放大 **图2** 光学显微镜观察显示，组织细胞S-100表达阳性 免疫组织化学染色（EnVision二步法） 低倍放大

**Figure 1** Optical microscopy findings. HE staining Histology showed a vaguely nodular lesion with a mixed inflammatory infiltration (Panel 1a). low power magnified Histocytes, individually or in large aggregates, interrupted the dense lymphoplasmacytic infiltrates (Panel 1b). low power magnified Large histocytes with intracytoplasmic lymphocytes and plasmocytes were characteristic findings (Panel 1c). medium power magnified **Figure 2** Optical microscopy showed histocytes expressed S-100 protein. Immunohistochemical staining (EnVision) low power magnified

颅内Rosai-Dorfman病常见于成人，呈孤立性或多灶性包块生长于硬脑膜，眶内或鼻、副鼻窦包块可扩展至鞍内和颅内。其影像学表现类似脑膜瘤，手术全切除或糖皮质激素治疗预后良好。组织形态学观察，低倍镜下可见病变呈结节状、淡染（图1a）；高倍镜下可见浆细胞，胞质淡染、核仁明显的组织细胞，以及淋巴细胞相互混杂浸润（图1b）；伸入运动，以及组织细胞胞质内可见完好的淋巴细胞和浆细胞，是其典型组织学特征（图1c），约70%的病例可见，有时不易见。组织细胞CD68和S-100蛋白表达阳性（图2），不表达CD1a。炎性浸润呈多克隆表现，提示Rosai-Dorfman病为反应性炎症反应而非真性肿瘤。

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