

· 临床病理报告 ·

原发性甲状腺功能减退症继发垂体增生伴高泌乳素血症

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【摘要】目的 报告1例原发性甲状腺功能减退症继发垂体增生伴高泌乳素血症患者,探讨其组织形态学、免疫组织化学表型、诊断与鉴别诊断、治疗及预后等临床病理学特点。**方法与结果**女性患者,29岁,临床表现为月经失调1年,溢乳3个月,头痛1周。MRI提示垂体瘤可能性大。遂行经鼻蝶鞍区占位性病变探查术。组织学形态观察,部分腺泡细胞明显增生,呈局灶性结节状。免疫组织化学染色,增生的腺泡细胞弥漫性表达突触素、促甲状腺激素,部分表达催乳素,不表达甲状腺转录因子-1,淋巴细胞散在表达白细胞共同抗原,Ki-67抗原标记指数约<1%。病理诊断为垂体增生,最终临床诊断为甲状腺功能减退症。持续服用左甲状腺素钠(优甲乐)100 μg/d,随访13个月,一般状况良好。**结论**垂体增生诊断困难,明确诊断须依靠临床病史、组织学形态特征和免疫组织化学表型,应注意与垂体腺瘤尤其是垂体微腺瘤相鉴别。

【关键词】 甲状腺功能减退症; 垂体; 增生; 高催乳素血症; 免疫组织化学; 病理学

Primary hypothyroidism presenting as pituitary hyperplasia with hyperprolactinemia

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【Abstract】 Objective To discuss the histological characteristics, immunohistochemical phenotypes, diagnosis and differential diagnosis, treatment and prognosis of one case of primary hypothyroidism presenting as pituitary hyperplasia concurrent with hyperprolactinemia. **Methods and Results** A 29-year-old female presented menoxenia for one year, galactorrhea for 3 months, and headache for one week. Head MRI demonstrated a sellar space-occupying lesion and a pituitary adenoma was suspected. Therefore, the patient underwent an exploratory surgery via transnasal-sphenoidal approach under general anesthesia. During the surgery the lesion was located in the right side of sella turcica. It was hard, tough and gray with poor blood supply. Under optical microscopy, the acinar cells showed a diffuse hyperplasia, with focal nodular expansion. The boundary between hyperplastic and normal acinus was ill-defined. By using immunohistochemical staining, the hyperplastic cells were diffusely positive for synaptophysin (Syn) and thyroid stimulating hormone (TSH), partially positive for prolactin (PRL), and negative for thyroid transcription factor-1 (TTF-1). Lymphocytes were scatteredly positive for leukocyte common antigen (LCA). Ki-67 labeling index was less than 1%. Pathological diagnosis was pituitary hyperplasia. The final clinical diagnosis was hypothyroidism. The patient took levothyroxine sodium (Euthyrox) 100 μg/d continuously, and was well during the 13-month follow-up. **Conclusions** Preoperative diagnosis of pituitary hyperplasia is difficult. Definite diagnosis could be made by clinical history, typical histopathological characteristics and immunohistochemical phenotypes. Differential diagnosis from pituitary adenoma, especially microadenoma, should be paid attention.

【Key words】 Hypothyroidism; Pituitary gland; Hyperplasia; Hyperprolactinemia; Immunohistochemistry; Pathology

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垂体增生(pituitary hyperplasia)分为生理性和病理性,是垂体分泌细胞对下丘脑分泌的激素刺激的反应。长期未治疗的甲状腺功能减退症患者垂体促甲状腺激素(TSH)细胞增生,女性可出现月经不调、溢乳和高泌乳素血症(HPPL)表现。本文报告1例以高泌乳素血症为主要表现的原发性甲状腺功能减退症继发垂体增生的青年女性患者,通过复习相关文献,对其组织形态学特征、免疫组织化学表型、诊断与鉴别诊断、治疗及预后等临床病理学特点进行探讨。

病历摘要

患者 女性,29岁,因月经失调1年、溢乳3个月伴头痛1周,于2014年6月4日入院。患者1年前哺乳期结束后出现月经周期延长(45~60 d)、经期延长(5~8 d),伴四肢无力、体重增加,未予特殊处理。3个月前挤压乳头时出现溢乳,乳汁呈白色、量少,未检测体温,至外院妇产科就诊,门诊检测性激素提示泌乳素(PRL)水平升高(具体数值不详),考虑为垂体原因,建议至神经外科就诊,门诊检查头部MRI提示垂体瘤。为求进一步诊断与治疗,至我院就诊。患者自发病以来,精神、睡眠、饮食尚可,大小便正常,体重增加约10 kg,体毛无明显变化。

既往史、个人史及家族史 患者既往身体健康。已婚、已育,月经初潮14岁、周期28~30 d、经期4~5 d、末次月经2014年5月10日。家族中无类似疾病患者。

入院后体格检查 体温37℃,脉搏57次/min,呼吸17次/min,血压114/70 mm Hg(1 mm Hg=0.133 kPa)。神志清楚,对答切题,高级神经功能无异常,颅骨无畸形,双侧瞳孔等大、等圆,直径3 mm,对光反射灵敏,视力左侧1.20、右侧0.50,视野左侧偶见暗点、右侧散在暗点,伸舌居中,无口角歪斜,无颈项强直,其余脑神经检查未见明显异常。四肢肌力5级、肌张力正常,腱反射对称引出,浅感觉无明显减退,病理征阴性,脑膜刺激征阴性。共济运动未见明显异常。体毛无变化,未检查乳房和外生殖器。

辅助检查 入院后完善各项实验室检查,血液一般检查和物理性质,以及肝肾功能试验均正常;垂体激素测定TSH>100 mIU/L(0.27~4.20 mIU/L)、PRL 401.54 nmol/L(15.23~74.09 nmol/L)、生长激素(GH)0.16 nmol/L(0.41~31.42 nmol/L)、黄体生成素

(LH)2.24 IU/L(卵泡期0~12.60 IU/L、排卵期0~95.60 IU/L、黄体期0~11.40 IU/L)、卵泡刺激素(FSH)3.95 IU/L(卵泡期0~12.50 IU/L、排卵期0~21.50 IU/L、黄体期0~7.70 IU/L)、皮质醇水平351.62 nmol/L(171.12~535.44 nmol/L);甲状腺功能试验游离三碘甲状腺原氨酸(FT₃)为2.05 pmol/L(3.10~6.80 pmol/L)、游离甲状腺素(FT₄)2.57 pmol/L(12~22 pmol/L)、三碘甲状腺原氨酸(T₃)0.67 nmol/L(1.30~3.10 nmol/L)、甲状腺素(T₄)为11.96 nmol/L(66~181 nmol/L)。头部CT和MRI检查显示,鞍区占位性病变,考虑垂体瘤可能性大(图1)。

诊断与治疗经过 临床诊断为垂体占位性病变,垂体瘤可能性大。遂于全身麻醉下行经鼻蝶鞍区占位性病变探查术。术中可见病变位于蝶鞍区内偏右侧,呈灰白色,大小约1.50 cm×1.00 cm×1.00 cm,质地硬韧,似有包膜,与硬脑膜边界尚清,血运不丰富,切取标本行组织病理学检查。(1)大体标本观察:切除标本为破碎组织数块,呈灰白和灰红色,大小约1.00 cm×1.00 cm×0.50 cm,质地较韧,未见明显包膜。经体积分数3.7%中性甲醛溶液固定,常规脱水、石蜡包埋,制备4 μm脑组织切片,分别行HE染色、免疫组织化学染色,以及网织纤维染色和高碘酸-雪夫(PAS)染色。(2)HE染色:光学显微镜观察,病变组织由呈片状分布的小至中等腺泡样细胞团构成(图2a),部分腺泡细胞明显增大,胞核呈圆形或卵圆形、染色质稍粗,胞质丰富、体积大而空(图2b),细胞呈局灶性结节状;部分区域腺泡结构基本正常(图2c),可见嗜酸性、嗜碱性和嫌色性细胞混杂排列;增大、增生的腺泡与正常腺泡界限不清、相互混杂。(3)免疫组织化学染色:采用EnVision二步法,检测用Ⅰ抗、Ⅱ抗、显色剂和染色系统参见表1。结果显示,垂体腺泡细胞增大、增生,弥漫性表达突触素(Syn),增生的腺泡细胞弥漫性表达TSH(图3a),部分表达PRL(图3b),其余腺泡细胞散在表达GH(图3c)、LH(图3d)、FSH(图3e)和促肾上腺皮质激素(ACTH)(图3f),不表达甲状腺转录因子-1(TTF-1);淋巴细胞散在表达白细胞共同抗原(LCA);Ki-67抗原标记指数<1%。(4)特殊染色:网织纤维染色可见腺泡基质结构完整(图4a),PAS染色呈阳性(图4b)。最终病理诊断为垂体增生。结合病理学检查结果,临床诊断为甲状腺功能减退症。遂转至内分泌科门诊治疗,遵医嘱持续服用左甲状腺素钠(优甲乐)100 μg/d。随访至今近

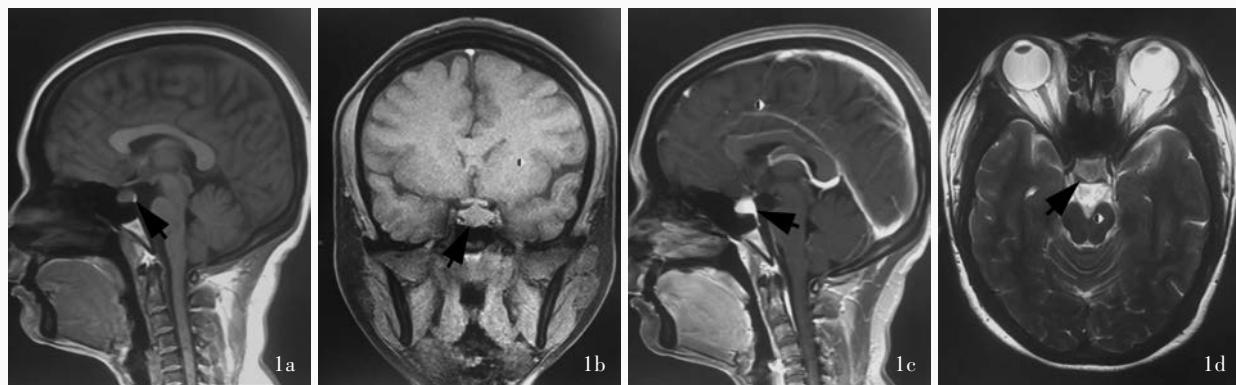


图1 头部MRI检查所见 1a 矢状位T₁WI显示,蝶鞍内团块状等信号影(箭头所示) 1b 冠状位T₁WI显示,垂体饱满、上缘膨隆,蝶鞍未见扩大,双侧颈内动脉海绵窦段部分被包绕(箭头所示) 1c 矢状位增强T₁WI显示,鞍内团块状信号明显强化(箭头所示) 1d 横断面T₂WI显示,病灶呈稍低信号,强度欠均匀(箭头所示)

Figure 1 Head MRI findings. Sagittal T₁WI showed an intrasellar mass with isointense signal (arrow indicates, Panel 1a). Coronal T₁WI showed pituitary gland was full with distention of the superior border sella turcica was not enlarged, and bilateral internal carotid artery cavernous segment was encased (arrow indicates, Panel 1b). Sagittal enhanced T₁WI demonstrated obvious enhancement of the lesion (arrow indicates, Panel 1c). Axial T₂WI showed a heterogeneous slight hypointense signal of the lesion (arrow indicates, Panel 1d).

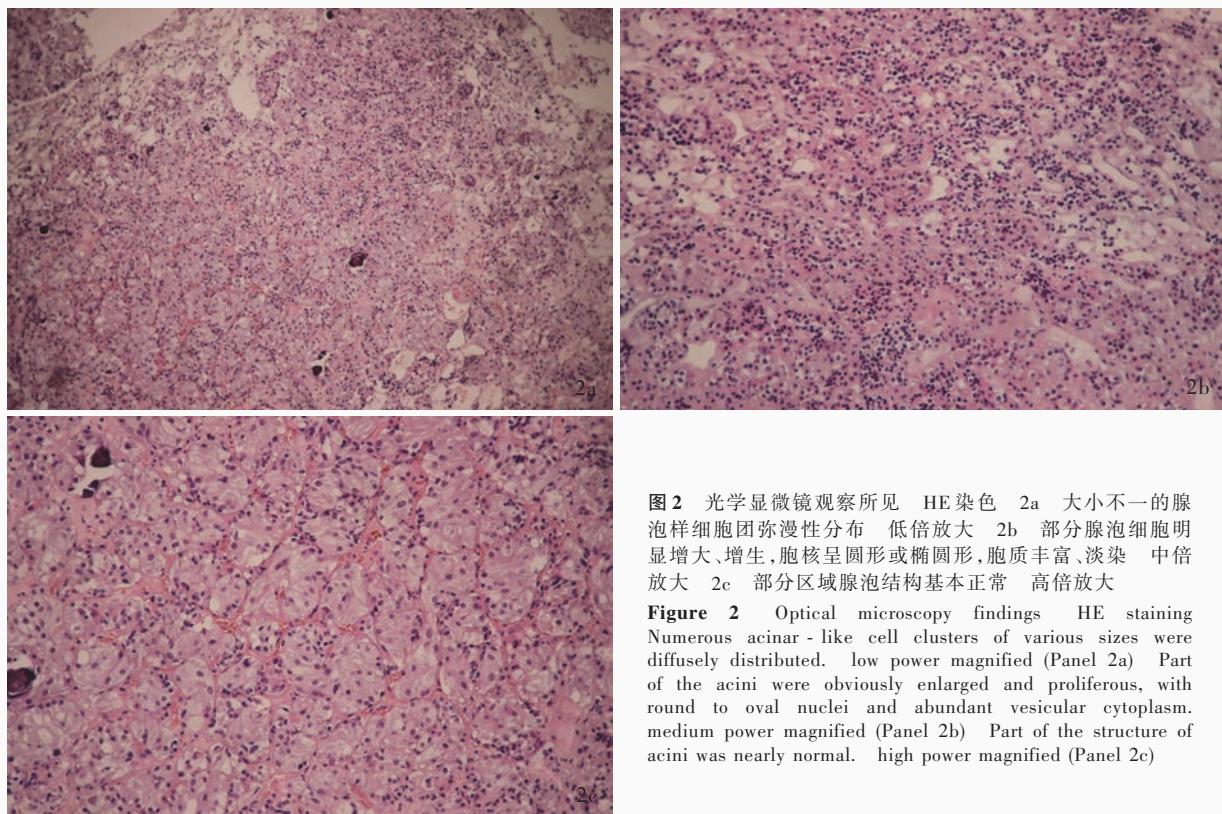


图2 光学显微镜观察所见 HE染色 2a 大小不一的腺泡样细胞团弥漫性分布 低倍放大 2b 部分腺泡细胞明显增大、增生,胞核呈圆形或椭圆形,胞质丰富、淡染 中倍放大 2c 部分区域腺泡结构基本正常 高倍放大

Figure 2 Optical microscopy findings. HE staining. Numerous acinar-like cell clusters of various sizes were diffusely distributed. low power magnified (Panel 2a) Part of the acini were obviously enlarged and proliferous, with round to oval nuclei and abundant vesicular cytoplasm. medium power magnified (Panel 2b) Part of the structure of acini was nearly normal. high power magnified (Panel 2c)

13个月,未再出现溢乳等内分泌系统症状,一般状况良好。

讨 论

垂体增生即为腺垂体细胞非肿瘤性细胞数目增加^[1-2],可以分为生理性、病理性、综合征相关性(如Addison病、Klinefelter综合征、Turner综合征等)

和特发性四种类型。甲状腺功能减退症致垂体增生主要是由于长期甲状腺激素水平低下对下丘脑的负反馈作用减弱,刺激垂体促甲状腺激素和催乳素细胞增生,出现高泌乳素血症,有时也可以完全无症状。

高泌乳素血症是临床最常见的下丘脑-垂体内分泌失调表现,研究显示,高泌乳素血症在桥本甲

表1 免疫组织化学检测项目表**Table 1.** Antibodies used for immunohistochemical examination

Antibody I	Clone ID	Company	Restorative procedure	Dilution ratio	Antibody II company	Dyeing system
Syn	SP11	Zhongshan (China)	Citric acid	Ready-to-use	Dako (America)	EnVision
TSH	QB2/6	Zhongshan (China)	EDTA	Ready-to-use	Dako (America)	EnVision
PRL	EP193	Zhongshan (China)	EDTA	Ready-to-use	Dako (America)	EnVision
GH	Rabbit polyclonal antibody	Zhongshan (China)	Not applicable	Ready-to-use	Dako (America)	EnVision
LH	Rabbit polyclonal antibody	Zhongshan (China)	EDTA	Ready-to-use	Dako (America)	EnVision
FSH	Rabbit polyclonal antibody	Jiehao (China)	EDTA	Ready-to-use	Dako (America)	EnVision
ACTH	B427	Zhongshan (China)	Not applicable	Ready-to-use	Dako (America)	EnVision
TTF-1	8G7G3/1	Zhongshan (China)	EDTA	Ready-to-use	Dako (America)	EnVision
LCA	RP2/18	Zhongshan (China)	Citric acid	Ready-to-use	Dako (America)	EnVision
Ki-67	K2	Zhongshan (China)	Citric acid	Ready-to-use	Dako (America)	EnVision

Syn, synaptophysin, 突触素; TSH, thyroid stimulating hormone, 促甲状腺激素; PRL, prolactin, 泌乳素; GH, growth hormone, 生长激素; LH, luteinizing hormone, 黄体生成素; FSH, follicle stimulating hormone, 卵泡刺激素; ACTH, adrenocorticotrophic hormone, 促肾上腺皮质激素; TTF-1, thyroid transcription factor - 1, 甲状腺转录因子 - 1; LCA, leukocyte common antigen, 白细胞共同抗原; EDTA, ethylenediaminetetraacetic acid, 乙二胺四乙酸

状腺炎亚临床期甲状腺功能减退和甲状腺功能减退症患者中的发生率分别为 11.1% 和 42.4%^[3-4], 在诊断明确的甲状腺功能减退症患者中的发生率为 21%^[5]。因此, 绝经期前甲状腺功能减退症继发垂体增生的女性患者常伴高泌乳素血症, 临床表现为月经紊乱、溢乳。

影像学检查可以为明确诊断提供重要的辅助作用, 表现为鞍区球形占位效应, 一般以中线为主, 界限清晰, 垂体上缘膨隆, 高度增加。传统观点认为, CT 显示垂体增高 > 10 mm 伴或不伴鞍底侵犯、垂体柄偏移是垂体腺瘤的诊断标准, 因此, 在 CT 影像上弥漫性垂体增大与垂体腺瘤有时难以鉴别。MRI 显示垂体信号不均匀, 垂体柄偏斜。甲状腺功能减退症致垂体增生和垂体炎患者的 MRI 表现类似垂体腺瘤, 表现为明显的中央占位效应, 边缘可见受挤压的正常垂体。因此, 单纯依靠 CT 和 MRI 检查仍无法准确区分垂体增生与垂体腺瘤, 尤其是与垂体微腺瘤的鉴别诊断更难^[6-7]。大体标本观察, 病变组织多呈灰白和灰黄色, 质地较韧, 血运不丰富。组织学形态可见结节性增生和弥漫性增生, 结节性增生表现为腺泡扩张, 而细胞相对单一, 对周围组织无挤压, 界限清晰, 尤其在破碎组织标本中不易识别; 弥漫性增生表现为垂体细胞数目增加, 但无腺泡结构改变, 有时需行细胞计数以明确诊断。核分裂象罕见。垂体增生包括^[8-12]: (1) 生长激素细胞增生。组织学形态表现为弥漫性增生的嫌

色性和嗜酸性细胞; 免疫组织化学染色生长激素呈阳性, 可见于正常垂体、泌乳素腺瘤和促肾上腺皮质激素腺瘤, 罕见进展为生长激素腺瘤。(2) 泌乳素细胞增生。组织学形态可见弥漫性或结节性增生的嫌色性细胞, 偶伴钙化; 免疫组织化学染色泌乳素呈阳性, 可见于正常垂体、垂体腺瘤, 罕见进展为泌乳素腺瘤。(3) 促肾上腺皮质激素细胞增生。组织学形态表现为弥漫性或结节性增生的大空泡嫌色性细胞, 可见 Crooke 细胞; 免疫组织化学染色促肾上腺皮质激素呈阳性, 可见于正常垂体、生长激素腺瘤和促肾上腺皮质激素腺瘤, 可能进展为促肾上腺皮质激素腺瘤。(4) 促甲状腺激素细胞增生。组织学形态可见弥漫性增生的嫌色性细胞, 细胞伸长, 溶酶体增多; 免疫组织化学染色促甲状腺激素呈阳性。有文献报道, 增生的垂体细胞共同表达促甲状腺激素和泌乳素^[13], 可同时伴泌乳素细胞增生, 见于正常垂体、泌乳素腺瘤, 偶进展为促甲状腺激素腺瘤。(5) 黄体生成素/卵泡刺激素细胞增生。组织学形态表现为垂体轻度弥漫性增生, 细胞空泡化; 免疫组织化学染色黄体生成素/卵泡刺激素呈阳性。Ki-67 抗原标记指数均较低。网织纤维染色可见正常腺泡结构, 有助于区分正常垂体、增生的垂体与腺瘤。PAS 染色可见增生的促甲状腺激素细胞胞质溶酶体呈阳性。

典型的垂体增生具有独特的组织学形态和免疫组织化学表型, 但若标本破碎、细胞数目较少、临

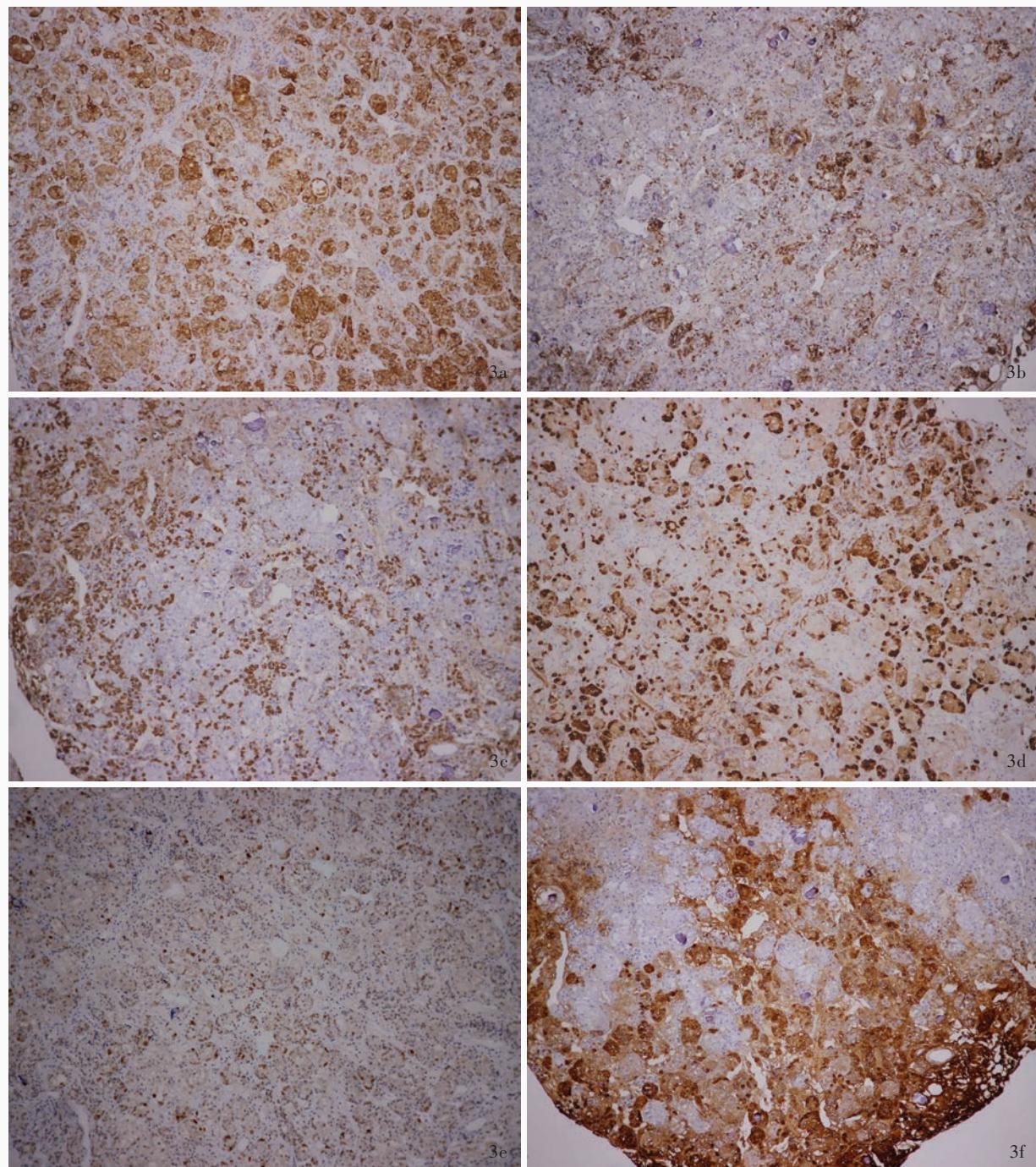


图3 光学显微镜观察所见 免疫组织化学染色(EnVision二步法) 低倍放大 3a 增大、增生的腺泡细胞胞质弥漫性表达TSH 3b 部分增大、增生的腺泡细胞胞质表达PRL 3c 部分腺泡细胞胞质表达GH 3d 部分腺泡细胞胞质表达LH 3e 部分腺泡细胞胞质表达FSH 3f 部分腺泡细胞胞质表达ACTH

Figure 3 Optical microscopy findings Immunohistochemical staining (EnVision) low power magnified The expanded acinar cells were diffusely positive for TSH (Panel 3a), and partially positive for PRL (Panel 3b), GH (Panel 3c), LH (Panel 3d), FSH (Panel 3e) and ACTH (Panel 3f) in the cytoplasm.

床病史不典型,诊断困难或易误诊,应注意与以下疾病相鉴别。(1)垂体腺瘤:是垂体前叶细胞形成的良性肿瘤,为蝶鞍内最常见肿瘤,多见于30~60岁女性。影像学表现为T₁WI低信号、T₂WI高信号。光

学显微镜观察,肿瘤细胞呈片状、条索状或乳头状排列,细胞呈圆形或多角形,可见异型性,核分裂象少见。以往根据肿瘤细胞染色性质分为嗜酸性细胞腺瘤、嗜碱性细胞腺瘤和嫌色性细胞腺瘤,目前

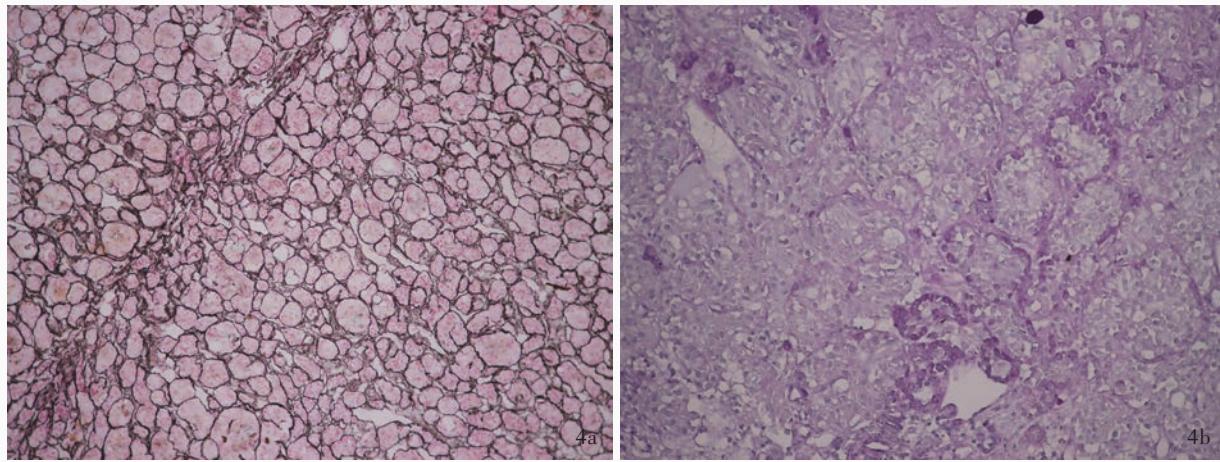


图4 光学显微镜观察所见 4a 腺泡细胞增生,但腺泡结构完整 网织纤维染色 低倍放大 4b 部分细胞PAS染色阳性
PAS染色 中倍放大

Figure 4 Optical microscopy findings Proliferation of the acini was seen, but the acinar structure was retained. Reticular fiber staining low power magnified (Panel 4a) Some cells were positive for PAS. PAS staining medium power magnified (Panel 4b)

根据电子显微镜观察和免疫组织化学染色分为分泌不同激素的细胞并以其所分泌的激素命名。肿瘤细胞表达突触素及相应激素,Ki-67抗原标记指数高于垂体增生,部分>3%;网织纤维染色显示腺泡基质结构破坏。垂体腺瘤大部分预后良好,部分为非典型垂体腺瘤,罕见垂体腺癌。(2)淋巴细胞性垂体炎:常表现为妊娠和分娩后鞍区占位性病变,伴垂体功能下降,偶出现某种激素缺乏。由于垂体柄受压,患者可能出现高泌乳素血症。几乎仅发生于女性。影像学表现为腺体对称性增大,垂体柄增粗,增强扫描可见病灶强化。光学显微镜观察显示,垂体组织中大量淋巴细胞浸润,散在浆细胞和组织细胞,可见有生发中心的滤泡形成、纤维组织增生、局部腺泡结构破坏。患者常伴其他内分泌器官如甲状腺、肾上腺炎症性改变。(3)正常垂体:组织学形态,正常垂体由呈片状或梁索状排列的上皮细胞构成,细胞间毛细血管丰富,腺泡内混有嗜酸性、嗜碱性和嫌色性细胞;免疫组织化学染色,6种激素均有表达。

目前认为,明确诊断垂体增生较为困难,因手术切除标本常是破碎组织和局部组织,不能反映垂体全貌,鉴别诊断须依靠组织病理学检查,且垂体增生进展为垂体腺瘤相对少见但也不能完全忽视,因此,临床考虑垂体增生时可先行试验性药物治疗,若出现视交叉压迫症状明显、视力和视野受损、内分泌症状进展、甲状腺素治疗无效时,可予手术探查以明确诊断^[14-16]。

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· 临床医学图像 ·

多激素腺瘤

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Plurihormonal adenoma

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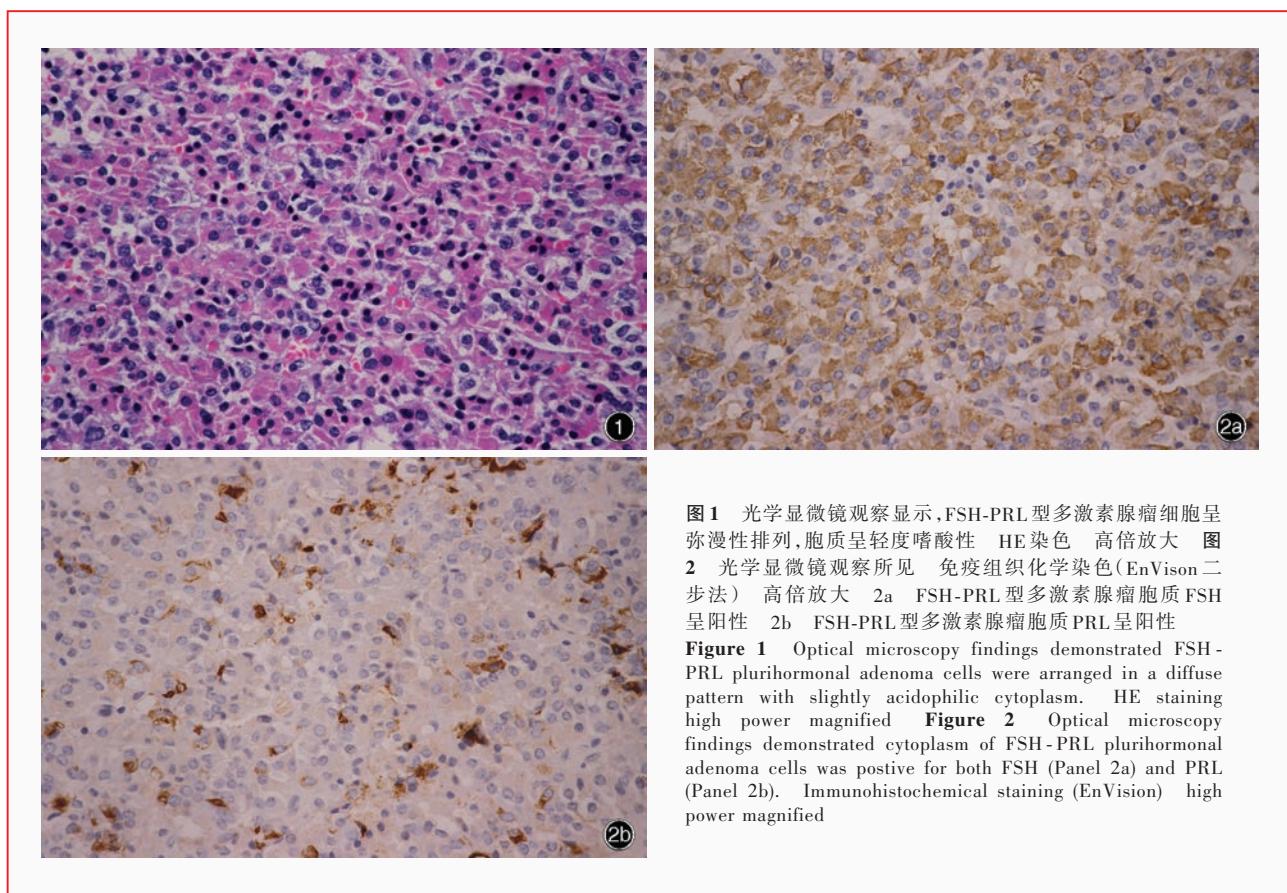


图1 光学显微镜观察显示,FSH-PRL型多激素腺瘤细胞呈弥漫性排列,胞质呈轻度嗜酸性 HE染色 高倍放大 **图2** 光学显微镜观察所见 免疫组织化学染色(EnVision二步法) 高倍放大 2a FSH-PRL型多激素腺瘤胞质FSH呈阳性 2b FSH-PRL型多激素腺瘤胞质PRL呈阳性

Figure 1 Optical microscopy findings demonstrated FSH-PRL plurihormonal adenoma cells were arranged in a diffuse pattern with slightly acidophilic cytoplasm. HE staining high power magnified **Figure 2** Optical microscopy findings demonstrated cytoplasm of FSH-PRL plurihormonal adenoma cells was positive for both FSH (Panel 2a) and PRL (Panel 2b). Immunohistochemical staining (EnVision) high power magnified

多激素腺瘤是临床少见的垂体肿瘤,常为大腺瘤,对1种及以上垂体激素产生免疫反应,且难以用正常生理学或发生机制解释。肿瘤一般呈嫌色性或轻微嗜酸性(图1),多形性肿瘤细胞少见,高碘酸-雪夫(PAS)染色常呈阴性。其中,静止性第三亚型腺瘤的特征性组织学形态为:肿瘤组织由梭形细胞和纤维间质构成,可见多形性肿瘤细胞和核分裂象。免疫组织化学染色呈多种激素联合表达,常见类型包括促肾上腺皮质激素-泌乳素(ACTH-PRL)型、卵泡刺激激素-泌乳素(FSH-PRL)型(图2)、卵泡刺激激素/黄体生成素-促肾上腺皮质激素(FSH/LH-ACTH)型。

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