

肾上腺皮质癌的综合治疗

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[摘要] **目的:**探讨肾上腺皮质癌临床及功能影像学 and 病理学特点, 提高肾上腺皮质癌诊治水平。 **方法:**分析肾上腺皮质癌患者的临床资料, 根据其临床表现、肾上腺内分泌功能测定、影像学特点和病理结果做出诊断, 进行手术治疗和米托坦药物治疗并随访。 **结果:**93例患者年龄11~76岁, 中位年龄48岁。男女比例1:1.2。24 h尿游离皮质醇(urinary free cortisol, UFC)高者86例, 促肾上腺皮质激素释放激素(adrenocorticotrophic hormone, ACTH)下降88例, 血浆皮质醇节律消失82例, 醛固酮升高31例, 性激素升高36例, 术前神经烯醇化酶(neuron specific enolase, NSE)升高27例, 胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)升高26例, 76例大剂量和小剂量地塞米松抑制试验均不被抑制。高血压62例, 典型Cushing综合征表现者81例。血糖升高54例, 低血钾症21例, 雄激素分泌者36例。肿瘤最大直径3~17 cm, 伴肾上腺中央静脉、肾静脉及下腔静脉瘤栓者6例, 手术至术后复发时间在1.2~5.0年。初发及随访中出现转移复发的56例, 其中肺转移13例, 肝转移17例, 腹膜后淋巴结转移9例, 腰椎转移7例, 卵巢转移3例, 腹壁及切口种植3例, 其他部位转移4例, 初发即远处转移者15例。行根治性切除术77例, 侵及同侧肾者做肾和肾上腺切除术11例, 肾上腺肿瘤并腔静脉瘤栓切除5例, 腔静脉部分切除3例。临床分期为I期39例, II期28例, III期16例, IV期10例。随访8~69个月, 手术5年以上的患者中有43例仍存活。 **结论:**肾上腺皮质癌早期诊断非常关键, 功能影像学检查结合临床特点及内分泌激素水平可确诊, 根治性手术是唯一有效的治疗方法, 米托坦可作为辅助治疗用于复发转移或无法手术治疗的, 肿瘤恶性程度高, 预后差。

[关键词] 肾上腺皮质癌; 核素成像; 病理; 米托坦; 预后

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Comprehensive treatment of adrenal cortical carcinoma

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ABSTRACT Objective: To investigate the clinical and functional imaging examination and pathological features of adrenocortical carcinoma (ACC), in order to improve the diagnosis and treatment of ACC. **Methods:** The clinical data of 93 patients with ACC were analyzed retrospectively. Their diagnosis, surgical treatment and follow-up of mitotane medicine therapy were made according to clinical manifestations, adrenal endocrine function determination, imaging examination characteristics and histopathological results. **Results:** Among the 93 patients, the age ranged from 11 to 76 years, with a median age of 48 years. The ratio of male to female was 1 : 1.2. Twenty-four hours urinary free cortisol (UFC) elevated in 86 cases, adrenocorticotrophic hormone (ACTH) decreased in 88 cases, blood F rhythm disappeared in 82 cases, and 31 cases of aldosterone increased. Thirty-six cases of sexual hormone increased. Neuron specific enolase (NSE) increased in 27 cases. Insulin-like growth factor-1 (IGF-1) increased in 26 cases. Seventy-six cases of high-dose dexamethasone suppression test (HDDST) and low-dose dexamethasone suppression test (LDDST) were not suppressed separately. There were 62 cases of hypertension, and typical Cushing manifestations in 81 cases. Blood glucose elevated in 54 cases. Hypokalemia was in 21 cases and androgen secretion increased in 36 cases. The maximum diameter of the tumor was 3 - 17 cm, with 6 cases of adrenal central vein, renal vein and inferior vena cava tumor thrombus. The recurrence time was 1.2 - 5.0 years after operation. Metastasis and recurrence were in 56 cases during the follow-up, lung metastasis in 13 cases, liver metastasis in 17 cases, retroperitoneal lymph node metastasis in 9 cases, lumbar metastasis in 7 cases, ovarian metastasis in 3 cases, abdominal wall and incision implantation in 4 cases. Fifteen cases with distant metastasis. Seventy-seven patients were treated with radical adrenalectomy, and the other patients were treated with renal and adrenal resection on the same side of the kidney. There were 5 cases of adrenal tumor with vena cava tumor thrombus in the removal of the tumor, and the other for the partial resection of the vena cava in 3 cases. Regarding the clinical stage,

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stage I was in 39 cases, stage II in 28 cases, stage III in 16 cases and stage IV in 10 cases. The patients were followed up for 8 – 69 months, and 43 patients survived more than 5 years. **Conclusion:** Function imaging combined with clinical features and endocrine hormone levels have important roles in ACC early diagnosis. Radical excision is the only effective treatment. Adjuvant or adjuvant mitotane drug therapy can be used for the treatment of recurrence and metastasis ACC patients. ACC is a tumor with high malignancy and poor prognosis.

KEY WORDS Adrenocortical carcinoma; Nuclear imaging; Pathology; Mitotane; Prognosis

肾上腺皮质癌罕见,临床表现差异较大,儿童及中年发病多见,涉及全身多个系统的内分泌检查异常,临床预后差,病死率高。北京协和医院泌尿外科2008年至2017年共收治肾上腺皮质癌患者93例,本研究对其临床表现、内分泌检查特点、功能影像学检查特征及预后进行分析,旨在探讨肾上腺皮质癌的疾病规律及诊治原则。

1 资料与方法

1.1 一般资料

93例患者,年龄11~76岁,主要发病年龄段集中在40~50岁,中位年龄48岁(图1),男女比例1:1.2(42:51)。肿瘤发生于右侧肾上腺区47例,左侧者32例,双侧者14例。诊断时初次原发肾上腺皮质癌患者78例,复发转移患者15例。

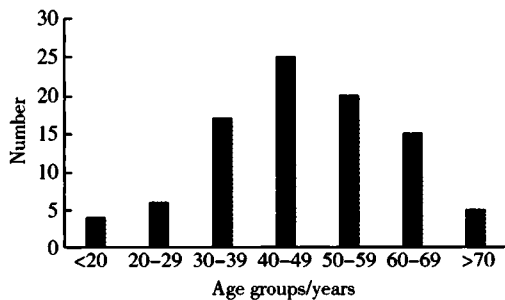


图1 肾上腺皮质癌年龄分布特点

Figure 1 Characteristic of age groups distribution in adrenal cortical adenocarcinoma

1.2 临床表现

肾上腺皮质癌患者累及肾上腺皮质的球状带、束状带和网状带,肿瘤较大也会挤压肾上腺髓质使其受累,其主要的临床表现为肥胖(91.4%)、Cushing体貌(87.1%)、疲乏(81.7%)、女性月经异常(84.3%)、下腹部及大腿根部皮肤紫纹(69.9%)、骨质疏松(57%,表1)。患者有典型Cushing综合征表现者81例,高血压62例,血糖水平升高54例,低血钾症21例,雄激素分泌异常者36例。

1.3 肾上腺内分泌相关检查

24 h尿游离皮质醇(urinary free cortisol, UFC)高者86例(92.5%),促肾上腺皮质激素释放激素

(adrenocorticotrophic hormone, ACTH)下降84例(90.3%),血浆皮质醇节律消失82例(88.2%,表2),醛固酮升高31例,性激素升高36例,术前神经烯醇化酶(neuron specific enolase, NSE)升高27例,胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)升高26例,76例大剂量和小剂量地塞米松抑制试验均不被抑制。

表1 肾上腺皮质癌常见的临床症状和体征特点

Table 1 Signs and symptoms of adrenal cortical adenocarcinoma

Signs and symptoms	Percentage/%
Obesity	91.4
Hypertension	66.7
Diabetes	77
Central obesity	76
Tired	81.7
Muscle atrophy	71
Hypertrichiasis and hairy	72
Abnormal menstruation and hyposexuality	43/51
Purple grain	69.9
Full moon face	67
Osteoporosis	57
Bruise	48
Skin color deepened	46
Mental change	44
Edema	43
Headache	37
Poor wound healing	40

1.4 影像学检查

93例患者均行腹盆腔增强CT或MRI,以及B超检查,91例患者行生长抑素受体——奥曲肽(octreotide)显像检查,76例患者行MIBG显像检查,21例患者行PET-CT检查。肿瘤最大直径3~17 cm,伴肾上腺中央静脉、肾静脉及下腔静脉瘤栓者6例。

2 结果

入院患者首次治疗均采用手术方式,术后有复发者采用内科综合治疗。手术至术后复发时间在1.2~5.0年。初发及随访中出现转移复发的56例,其中肺转移13例,肝转移29例,局部肾周筋膜

复发者 11 例,腹膜后淋巴结转移 9 例,腰椎转移 7 例,卵巢转移 3 例,腹壁及切口种植 3 例,其他部位转移 4 例,初发即远处转移者 15 例。18-氟脱氧葡萄糖 PET-CT 扫描早期发现恶性肿瘤,改善患者的病情分期,尽早手术可能获得较好的预后,21 例患者选择 PET-CT 检查,19 例标准摄取值明显升高(图 2)。93 例患者行根治性切除术 77 例,范围包括肾上腺肿物,肾门区以上所有脂肪组织。侵及同侧肾者做肾和肾上腺切除术 11 例,肾上腺肿瘤并腔静脉癌栓切除 5 例,腔静脉部分切除 3 例。肾上腺皮质癌大体标本多体积大,切面呈咖啡色和黄色交替存在(图 3),组织病理学提示核增值指数 Ki-67 在 81 例患者中升高,Ki-67 > 10% 则临床预后更差。临床分期为 I 期 39 例,II 期 28 例,III 期 16 例,IV 期 10 例。口服米托坦治疗的 36 例患者中,每天 20 ~ 30 mg/kg,分 3 ~ 4 次口服,从小剂量开始逐渐增大到最大耐受量,每天 2 ~ 6 g,如出现不良反应,则减少剂量,在可耐受剂量维持。米托坦可使肾上腺皮质功能亢进症状明显缓解,肿瘤缩小 10% ~ 30%,对于不能手术切除或有远处转移的肾上腺皮质癌有效,客观有效率为 46%,但有腹泻、皮疹、食欲下降、肝功能异常、肾上腺皮质功能不全等不良反应,均行药物对症治疗。患者在尿皮质醇浓度下降、有肾上腺皮质功能不全时,均予以氢化可的松口服治疗,定期检测肝肾功能、血常规及肾上腺内分泌检查,行胸腹盆 CT 复查,随访 8 ~ 69 个月,手术后随访 5 年以上的患者中有 63 例仍存活。

表 2 肾上腺皮质癌临床和激素水平特征

Table 2 Clinical data and adrenocorticotropic hormone levels of adrenal cortical adenocarcinoma

Parameters	Results
Age/years	48.1 ± 2.1
BMI/(kg/m ²)	26.3 ± 1.4
Maximum diameter of adrenal mass/cm	7.4 ± 0.7
24 h UFC/μg	234 ± 39
8:00 ACTH/(ng/L)	4.5 ± 4.1
F/(μg/dL)	401.2 ± 17.1
Control UFC (HDDST μg/24 h)	161 ± 46
SBP/mmHg	149.3 ± 5.2
DBP/mmHg	93.4 ± 1.7
Blood glucose level/(mmol/L)	7.18 ± 0.3
HbA1c/%	8.6 ± 1.4
Total cholesterol/(mmol/L)	5.71 ± 0.27
Triglyceride/(mmol/L)	2.0 ± 0.3

BMI, body mass index; ACTH, adrenocorticotropic hormone; HDDST, high-dose dexamethasone suppression test; UFC, urinary free cortisol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

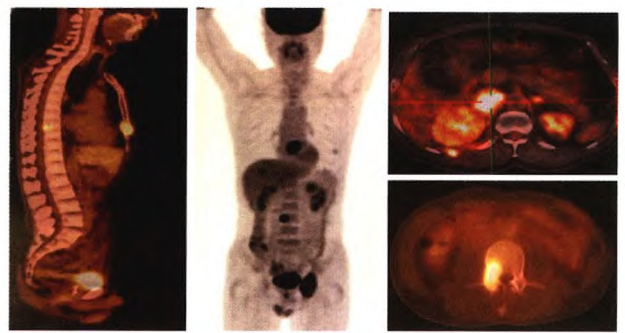


图 2 18-氟脱氧葡萄糖 PET-CT 显示肝、淋巴结、脊柱及胸骨多发转移

Figure 2 ¹⁸F-FDG PET-CT Showed multiple metastases of liver, lymph nodes, spine and sternum



A, enhanced CT showed of massive cortical carcinoma of the adrenal region; B, general specimen of adrenocortical carcinoma; C, high power microscopic appearance of an adrenal cortical carcinoma (×200).

图 3 肾上腺皮质癌大体标本及病理特点

Figure 3 Gross and pathological features of adrenocortical carcinoma

3 讨论

肾上腺皮质癌(adrenocortical carcinoma, ACC) 罕见,发病率为百万分之一至百万分之二^[1]。ACC 具有双峰年龄分布特点,高峰发病率在儿童早期和 40 ~ 50 岁,男女比例约为 1 : 1.5^[2]。本研究的患者中位年龄在 48 岁,是因为北京地区的患儿集中在儿童专科医院就诊。儿童的发病率在巴西南部最高,患病率高达 0.27%。ACC 多数散发,也常见于一些遗传综合征(如 Li-Fraumeni 综合征, Beckwith-Wiedemann 综合征和 MEN1^[3]),或由于特异性 TP53 基因种系突变(17p13 染色体, R337H)和胰岛素样生长因子-2 基因易位(11p15)。

本研究患者主要的临床特点是尿皮质醇产生过量;患者脱氢表雄酮(dehydroepiandrosterone, DHEA)升高,累及球状带束网带的激素异常,神经烯醇化酶升高,奥曲肽显像表达。约 70% 患者有糖皮质激素过量的表现,或伴有男性化,皮质醇过度分泌相关的体征和症状[包括体重增加、虚弱(主要是近端肌肉)、高血压、精神紊乱、多毛症、向心性肥胖、紫色条纹、水牛背、锁骨上脂肪增多、高血糖症和低钾血症];醛固酮分泌性肿瘤可能存在高血压、乏力和低钾血症;雄激素分泌性肿瘤可能诱发多毛症和月经紊乱,与文献报道基本一致^[4]。在男性中,分泌雌激素的肿瘤可能诱发男性乳房发育和睾丸萎

缩。与肿瘤负荷相关的症状,包括腹痛、腹部包块、腔静脉瘤栓导致的双下肢水肿、背痛、早饱和体重减轻^[5-6],此外,还可能合并乳腺癌、骨肉瘤或脑瘤(Li-Fraumeni's综合征)、多种激素分泌综合征,异位激素分泌综合征。 >4 cm的不规则边缘或内部异质的功能性肿瘤应考虑ACC^[7],如怀疑淋巴结或肝转移需行增强CT评估。平扫CT把10 HU作为区分良性和恶性肾上腺肿瘤的界限,增强的CT在15 min时洗脱值大于60%,肿瘤良性可能性大^[7],MRI比CT扫描更清楚地记录局部侵犯和下腔静脉受累^[8-9],无论是CT还是MRI扫描,使用肾上腺区薄扫确定大小、异质性、脂质含量、对比度清除和边缘特性。当原发肿瘤最大径大于4 cm并且怀疑为癌时,评估转移性疾病和局部浸润推荐胸腹盆CT或MRI,联合内分泌功能检查,断层CT可使大多数ACC患者得到明确诊断。ACC患者的肾上腺肿瘤体积多 >11 cm,而大多数腺瘤患者肿瘤体积 <5 cm。肿瘤直径在3~10 cm时,需慎重诊断。ACC患者都具有高水平的18-氟脱氧葡萄糖摄取,用美托咪酯作为示踪剂进行PET-CT检查,美托咪酯可以与肾上腺皮质上的CYP11B酶特异性结合,CYP11B酶可以催化皮质醇合成,这种方法特异性很高。ACC患者要进行胸部CT明确有无肺转移。本研究患者初诊和随访中发现,18-氟脱氧葡萄糖PET-CT扫描无法明确患者的病情分期,肾上腺肿块活检的价值不大,细针穿刺活检的作用亦有限,而且可能会引起细针穿刺部位发生肿瘤细胞转移。仅在以下两种情况下进行细针穿刺可能获益:第一是部分患者发生肿瘤转移,失去了外科手术治疗的机会,且内分泌检查和美托咪酯PET-CT扫描无法明确诊断;第二是怀疑肾上腺肿物没有内分泌活性,且患者有肾上腺外恶性肿瘤的病史,细针穿刺活检能够确定治疗方案。如果肿瘤大于4 cm或与不规则边缘和/或局部浸润和其他恶性成像特征,应怀疑恶性肿瘤。患有局部肾上腺皮质癌推荐手术切除肿瘤,去除相邻淋巴结。通常病理上采用Weiss标准判定恶性的特点:高核分级,有丝分裂率 $>5/50$ 高倍视野,非典型有丝分裂,嗜酸性肿瘤细胞质($>75\%$),弥漫性结构模式($>33\%$)与广泛的纤维和小梁带,融合性坏死灶,静脉受侵袭,窦状间隙受侵袭,包膜受侵袭。如果患者有阳性边缘,包膜不完整,大体积或高级别则局部复发的风险高,可以考虑米托坦辅助治疗,并使用替代剂量的氢化可的松以防止肾上腺

功能不全。用于晚期肾上腺癌的全身治疗的选择是米托坦单一疗法或顺铂、卡铂、依托泊苷、多柔比星、链脲霉素和米托坦的组合。对于晚期或转移患者米托坦单一疗法部分反应率最多为20%~40%。目前,米托坦治疗转移性肾上腺皮质癌的最佳剂量和持续时间尚未标准化,给药量的40%~60%由胃肠道吸收,一次给药3~4 h后血中药物浓度达高峰。给药剂量10%~25%以可溶于水的代谢物随尿排出,60%以原形从粪便中排出。肾上腺癌术后复发比较常见,及时发现肿瘤复发调整后续治疗有助于延长患者生存期。因此,推荐每3个月进行一次影像学检查(胸部CT和腹部的CT或者MRI),同时联合检测血清皮质醇水平^[10]。约3%的ACC患者有Lynch综合征,可接受遗传筛查^[11]。术后随访2年后,可以逐渐延长随访影像学检查的间期。

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