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◇临床医学◇

外阴颗粒细胞瘤3例及文献回顾

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摘要: **目的** 探讨女性外阴颗粒细胞瘤(granular cell tumor,GCT)临床特征、诊断、治疗及预后。**方法** 回顾性分析2018年1月至2019年11月中国科学技术大学附属第一医院(安徽省立医院)妇科收治的3例女性外阴GCT病人的临床资料。**结果** 3例病人年龄分别为31岁、49岁、39岁,外阴包块均无症状,其中病例1为妊娠期发现外阴包块,产后无明显缩小就诊,另2例为无意中发现外阴包块且随访期间进行性增大就诊。病例1术前未行活检,因包块与周围正常组织无明显边界,同时切除包块外正常组织0.5~1.0 cm;病例2先于门诊行单纯外阴包块切除术,术后病理提示切缘阳性入院再次扩大手术范围,达原切缘外1~2 cm;病例3术前外阴活检提示GCT,行外阴包块局部扩大切除术,达病灶外1~2 cm。3例病人均顺利出院,术后分别随访20个月、14个月、2个月未复发。**结论** 女性外阴GCT发病率低,多无临床症状,易被忽视。虽多为良性病变,但有少数有复发或恶变可能,一旦发现外阴部包块应重视,必要时外阴活检确诊,一旦诊断,及时手术治疗,并定期随访。

关键词: 颗粒细胞瘤; 外阴肿瘤; 包块切除; 女性

Granular cell tumor of vulva: 3 case reports and literature review

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Abstract: **Objective** To investigate the clinical characteristics, diagnosis, treatment and prognosis of the female vulvar granulosa cell tumor (GCT).**Methods** The clinical data of three female patients with granulosa cell tumor of vulva who were admitted to the Department of Gynecology, the First Affiliated Hospital of China University of science and Technology (Anhui Provincial Hospital) from January 2018 to November 2019 were analyzed retrospectively.**Results** The age of the three patients were 31 years old, 49 years old and 39 years old, the vulvar masses were all asymptomatic. Case one′s vulvar mass was found during pregnancy, and there was no obvious reduction after childbirth. The other two patients′s vulvar mass were found inadvertently and increased during follow-up. Case 1 was not biopsied before surgery, because there was no obvious boundary between the mass and surrounding normal tissue, and 0.5~1.0 cm of normal tissue outside the mass was removed at the same time. Case 2 underwent with an outpatient operation, and the operation scope was expanded again due to positive pathological margin after operation,1~2 cm outside the original cutting edge. Case 3 underwent local extended resection of vulvar mass according to the vulva biopsy before the operation, reaching 1~2 cm outside the lesion. All patients were discharged successfully. The patients were followed up for 20 months, 14 months and 2 months without recurrence respectively.**Conclusions** The incidence of granulosa cell tumor of vulva is low, most of them have no clinical symptoms and easy to be ignored. Although most of them are benign lesions, a few of them are likely to recur or become malignant. Once the mass of vulva is found, we should pay more attention to it. If necessary, the vulva biopsy should be confirmed. Once the diagnosis is made, timely surgical treatment should be carried out and regular follow-up should be carried out.

Key words: Granular cell tumor; Tumor of vulva; Mass removal; Femininity

颗粒细胞瘤(granular cell tumor,GCT)是一种含有嗜酸性颗粒的软组织肿瘤,可发生于任何年龄。该肿瘤多发于头颈部、躯干和四肢的皮肤及皮下组织,外阴部少见。本研究回顾性分析3例诊治于中国科学技术大学附属第一医院(安徽省立医院)的外阴GCT病人的相关资料,并结合相关文献进行分析。

1 病例资料

病例1:女性,31岁,因“自觉外阴赘生物1年余”入院,无疼痛及瘙痒等症状。病人发现包块时为孕期,未予治疗,剖宫产术后9月,包块未缩小。查体:右侧大阴唇上段近阴阜处可见长径约4 cm占位,无压痛及反跳痛,活动度尚可。2018年5月9日

外阴B超提示右侧会阴软组织内见26 mm×24 mm×21 mm低回声,边界尚清,其内未见明显血流信号。考虑为外阴良性肿瘤,于2018年5月9日行外阴包块切除术,术前未明确病理性质,仅按外阴良性肿瘤行单纯外阴包块切除术,包块无明显边界,同时切除包块外正常组织0.5~1.0 cm。术后病理提示外阴GCT,随访20个月,无复发。

病例2:女性,49岁,因"自觉外阴部包块并进行性增大1年"入院,无疼痛及瘙痒。查体:左侧大阴唇外侧长径约1 cm占位,无压痛及反跳痛。于2018年1月5日在门诊行外阴包块切除,术后病理提示外阴GCT,切缘见肿瘤累及,于2周后再次手术,扩大手术范围至原切缘外1~2 cm沿包块外缘切除包块,术后病理提示切缘阴性。随访14个月无复发。

病例3:女性,39岁,因"自觉会阴部包块并进行性增大半年"入院,无外阴部瘙痒、疼痛、发热。病人无疫水、疫情等接触史,无药物、毒物等接触史,无外伤手术史,无药物过敏史,否认家族史。查体:阴阜正中可见长径约2.5 cm凸起,边界清楚,压痛阴性,活动度尚可。2019年11月5日外阴活检提示外阴鳞状上皮增生伴非典型增生,局部糜烂,黏膜下多量泡沫样多边形,圆形细胞浸润,不排除颗粒性肌母细胞瘤。遂于2019年11月22日在全身麻醉下行外阴局部扩大切除,包块外1~2 cm,术后病理提示外阴GCT。术后随访2月无复发。具体见图1。

本研究符合《世界医学协会赫尔辛基宣言》相关要求,病人或近亲属已签署知情同意书。

2 讨论

GCT也称颗粒细胞肌母细胞瘤,临床少见,绝大多数为良性,来源于神经鞘。该肿瘤可发生于身体的任何部位,最常见的部位为舌、躯干、消化系统等,外阴GCT少见,占所有GCT的7%~16%,多见于阴唇,偶见于阴蒂。Dupuis、Coard[1]对122例GCT病人进行总结,男女比例为1∶4.3,各年龄阶段均可发病,年龄范围为5 d至82岁,平均年龄34.4岁,16岁或16岁以下的儿童占14.6%。GCT缺乏典型临床表现,常于体检或其他手术中被偶然发现[2-3],有些表现为疼痛、瘙痒症状[4],多为实性的皮下或黏膜下结节,表面可形成浅表溃疡。本研究中3例病人术前无症状,均为偶然发现。

生物学性质:GCT分为良性GCT及恶性GCT,恶性GCT约占2%[5]。目前恶性GCT的诊断标准尚无共识,Fanburg-Smith等[6]于1998年提出的恶性GCT 6个诊断标准:肿瘤进行性生长;肿瘤短期内生长迅速;肿瘤长径>5 cm;肿瘤存在早期局部区域复发或转移;组织学表现为坏死、梭形细胞、空泡状核及大核仁、核分裂象> 2/10HPF、高核质比和多形性,符合其中1个条件视为组织学不典型,符合3个或以上条件者视为组织学恶性。本研究中3例病人均不具有上述特征,为良性GCT。Nasser等[7]简化了上述标准,仅根据坏死和/或有丝分裂的存在对这些肿瘤进行分类,但需在病理报告中描述异常结果。Harou等[8]认为恶性GCT常见特征为:体积较大(>4 cm)、快速生长,组织学上表现为有丝分裂、核异型性、坏死和血管侵犯。Battistella等[9]发现有些良性GCT也有血管、皮下组织、神经的侵犯,但没有影响肿瘤的生物学行为,故局部侵袭性生长尚不足作为GCT良、恶性的鉴别要点。一些恶性肿瘤在组织学上与良性肿瘤相同,但通过转移显示出恶性潜能。Schmidt等[10]报道的7例恶性肿瘤中,有3例组织学为良性GCT。

发生机制:GCT发生机制尚不清楚,该肿瘤好发于女性,尤其是绝经前女性[11],Svenningsen、Kanje[12]认为女性激素可能参与促进女性干细胞向施万细胞的分化,Fishbein等[13]也提出了相似理论。肿瘤多发生于富于肌肉和神经的软组织,以舌部发病率最高,可能是继发于刺激性、急和/或慢性创伤性事件引起的"修复性反应",类似于创伤性神经瘤[14-15]。施万细胞敏感,是外周神经系统发育和创伤后修复的关键因素[16]。不同的刺激例如不同基因的抑制和过度表达、TNF、细胞因子等促炎分子的分泌等,都可以引起施万细胞过度再生[17]。另有报道GCT与Noonan综合征、神经纤维瘤Ⅰ型等综合征有关[5],他们的Ras/MAP通路中都存在一种异常信号,这种信号可以促进细胞分化、增殖和肿瘤形成[18],可能与肿瘤发生有关。

也有GCT与遗传相关的报道。Schrader等[19]报道一例多发性GCT病人PTPN11基因突变,Sidwell等[20]也报道了一例Noonan综合征伴有阴囊GCT病人,PTPN11上出现了非特异性突变,PTPN11基因的变异可能参与了GCT的发生。郑娇等[21]报道1例恶性GCT病人经过全基因组二代测序,发现BRD7存在功能缺失突变,BRD7很可能成为一个新的肿瘤抑制基因位点,另有1例恶性GCT报道发现CDKNA(P16)基因缺失[22]。Kardhashi等[23]报道了一例外阴GCT家族聚集的病例,一位60岁的病人和她32岁的外甥女均发生左大阴唇GCT。遗传因素是否在GCT尤其是恶性GCT发生中发挥作用,还需更多的研究。

诊断与鉴别诊断:因外阴GCT少见,且临床表现无特异性,术前很难确诊。在多发病灶病人中,92%伴有外阴病变,因此在第一次就诊和随访期间

应评估外阴情况。临床医生应详细记录病史,并进行全面体检和辅助检查以排除多发病变。B超、CT、MRI是最常用的影像学检查方法,有助于辅助检查,组织病理学检查是确诊该病的唯一手段。典型的组织学特征结合免疫组化标记s-100、NSE及CD68均强阳性等特征可以明确诊断。与良性肿瘤相比,非典型和恶性GCT中Ki67的增殖指数和p53的免疫抑制明显高于良性肿瘤[24-26]。应与外阴结节性实性良性无痛性病变,如脂肪瘤、纤维瘤、汗腺瘤、外阴癌等鉴别。外阴GCT和卵巢GCT易于鉴别,起源不同、发生部位不同,外阴GCT起源于神经鞘,多位于皮下或黏膜下,卵巢GCT是粒层细胞瘤,属于性索-间质肿瘤,多位于卵巢组织上。

治疗:手术完整切除GCT肿瘤是主要治疗方案,但由于肿瘤一般浸润性生长,无包膜且有恶变倾向,个别复发的病例主要是因为首次治疗未能完整切除病灶,所以主张适当扩大切除范围[27]。边缘无残留复发率2%~8%,残留的复发率20%[28]。卢烨等[29]建议手术切除的范围应包括肿瘤边缘正常组织1~2 cm。切除肿瘤的边缘应仔细检查,如果手术边缘有肿瘤残留,应进行更广泛的局部切除。术前活检细胞学诊断明确性质或术中冰冻检查了解切缘情况可为术中确定手术范围提供依据。本研究中只有病例3术前穿刺活检病理明确为GCT,术中行外阴局部扩大手术切除;另2例病人术前未明确病人病理性质仅行单纯外阴病灶切除,其中病例2切缘阳性再次追加手术,病例1切缘阴性,随访20月未复发。非典型GCT以扩大切除治疗为主,恶性GCT应行根治性局部手术,术后予以定期复查或系统化治疗。GCT具有通过血行和淋巴播散转移的能力,最常见的转移部位包括肺、淋巴结和骨[30],脾脏、心脏、心包、中枢神经系统[31]、甲状腺、肠和胰腺等也有远处转移的报道。Schmidt等[10]建议在这些侵袭性GCT的病例中采用以下分期方法来检测或排除远处转移:超声(淋巴和肝转移)、胸部X光片、CT胸部/腹部/骨盆(肺、肝和成骨细胞转移)、骨显像(骨转移)。良性GCT不需辅助治疗,不典型及恶性外阴GCT术后辅助治疗经验不足。恶性GCT属于高度恶性肿瘤,约50%~70%病人出现转移或复发[32],局部区域广泛切除加必要的区域淋巴结清扫对于提高病人的生存质量仍是必需的手段,放疗[33]及化疗并不能改善其临床进程。但又有报道指出放射治疗有一定疗效,局部控制满意,随访16个月未复发[10]。

预后:GCT属于软组织肿瘤,其恶性程度较低,预后较好,在确诊时肿瘤往往尚未发生扩散及发展为中晚期。尽管为良性GCT,但易复发或恶变。良性GCT复发或恶变率1%~2%[34],局部复发通常在术后2年内出现,非典型和恶性GCT复发率50%。单发性病变复发率10.6%,多发性病变复发率在33.3%[35],因此在随访期间应评估生殖器外区域,特别是舌头和口腔。Fanburg-Smith等[6]认为恶性GCT的不良预后影响因素有局部复发、转移、老年、肿瘤14 cm。Kardhashi等[23]更强调肿瘤大小对预后的影响,年龄无差异。恶性GCT病人治疗后10年以上可发生转移,建议长期随访,对于多灶性疾病、非典型或恶性肿瘤、大型肿瘤应每6~12个月进行一次体检和影像检查。

总之,外阴GCT临床虽少见,即使是良性GCT也存在复发、恶变可能,临床上对于外阴包块均应重视,建议活检。术前充分评估,排除其他部位或器官有无受累。手术过程中应彻底切除肿瘤,建议切除范围为包块外1~2 cm,减少复发概率。临床医生与病理科医生互相沟通,术后密切随访。外阴GCT的发生发展是否与遗传变异有关,还需今后进一步的研究来论证。

(本文图1见插图1-2)

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