

子宫腺肌病恶变的诊治及注意事项

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子宫腺肌病(adenomyosis, ADS)是一种常见的妇科疾病,其特征性表现为子宫内膜腺体和间质异位于周围深肌层,伴有邻近肌层的增生肥厚的子宫肌层损害,常以月经过多、痛经、盆腔痛、子宫异常出血及宫体增大为主要症状。ADS在某些方面可表现出恶性特征,比如迅速增长、血管生成和侵袭。ADS在子宫内膜癌子宫切除标本中常见,但ADS恶变发病率低,以恶变为子宫内膜癌多见。其恶变机制尚不清楚,且术前诊断困难,确诊多依赖于术后病理。以手术治疗为主,辅以放疗、化疗。其预后研究尚不清楚。本文就ADS恶变的诊治相关研究进行综述。

1 流行病学与临床表现

ADS恶变少见,其恶变率目前尚无报道。1897年,Rolly报道了首例子宫腺肌病恶变为子宫内膜癌的病例,其后ADS恶变逐渐受到关注。其中绝大多数ADS恶变为子宫内膜腺癌发生在绝经后妇女,绝经前妇女恶变者更为罕见^[1]。

ADS恶变为子宫内膜癌缺乏特异性的临床表现,主要症状为异常阴道流血、经量增多、贫血、体重减轻等^[2]。与未恶变者比较,由于缺乏特异性临床表现,难以区分。原发性子宫内膜癌患者常伴有高血压、糖尿病、肥胖“三联征”。目前尚无相关研究表明,ADS恶变

与子宫内膜癌“三联征”之间的相关性。

2 子宫腺肌病恶变的病理诊断标准

对于由ADS恶变而来的子宫内膜癌,目前国际上公认病理诊断标准为Sampson标准和Scott补充标准^[2-3]。Sampson标准包括:①癌组织和异位内膜组织共存于同一病变中;②腺细胞和/或子宫内膜基质细胞存在支持ADS的诊断;③良性和恶性腺体结构间存在转化证据;④排除其他来源的肿瘤侵犯或转移^[2]。Scott补充标准为:显微镜下见异位内膜向恶性移行形态学证据,即同时存在正常内膜上皮、交界性、浸润性癌^[3]。Colman等^[4]在此基础上提出了ADS恶变的病理学诊断标准为:①正常位置子宫内膜或盆腔其他部位的内膜中无癌组织;②癌灶源自ADS区域的上皮,而非其他来源的肿瘤侵入;③在癌变的腺体周围可见子宫内膜间质包绕,以支持ADS的诊断。

3 子宫腺肌病恶变的危险因素及病理类型

基于ADS的低恶变率,目前缺乏大样本、多中心RCT研究,有多项队列研究就子宫腺肌病恶变的相关因素进行了研究^[5-10]。已有研究提出,绝大多数ADS恶变为子宫内膜腺癌发生在绝经后妇女,绝经前妇女少见^[1]。激素替代治疗史、伴发子宫平滑肌瘤和/或良性

子宫内膜增生可能均与 ADS 恶变存在相关性^[5-10]。

ADS 恶变为子宫内膜癌中最常见的是子宫内膜样腺癌,其次为浆液性癌、透明细胞癌和低分化腺癌^[11]。由 ADS 恶变所致浆液性子宫内膜上皮内癌(浆液性 EIC)是罕见的^[12-13]。有学者就 ADS 恶变所致子宫内膜癌与非 ADS 恶变所致子宫内膜癌 FIGO 分期及组织学分级状况进行了研究^[6,8-9,14],现有研究表明,无论是 ADS 恶变所致子宫内膜癌,还是非 ADS 恶变所致子宫内膜癌,其 FIGO 分期及组织学分级没有显著差异,但 ADS 恶变所致子宫内膜癌似乎更倾向于低分期、低组织学分级。

4 子宫腺肌病恶变的发病机制

ADS 在某些方面表现出恶性特征,比如迅速增长、血管生成和侵袭。恶性疾病进展鲜少发生^[2]。目前认为,ADS 子宫内膜上皮转变至恶变前单层肿瘤细胞,最终发展为不同程度的癌变^[2]。然而,引起肌层细胞转化及随后调控的具体分子尚不明确。病理学及分子机制的合理性尚缺乏有力证实。

已有一些数据表明,在 ADS 中存在遗传改变、突变分析和特异性抑癌基因的失活,这些改变可能与其恶变相关^[15-17]。Goumenou 等^[15]首次报道,在 ADS 中存在杂合性缺失(LOH)。DNA 错配修复基因(hMSH 2、hMLH 1)、p 16 Ink 4(CDKN 2A、细胞周期蛋白依赖性激酶抑制剂 2 A)和 GALT(半乳糖-1-磷酸尿苷酰转移酶 GALT)基因与 ADS 发生和发展有关^[15]。ADS 间质 Bcl-2 的表达维持在较低水平,可能会对异位内膜组织的生长和存活产生负面影响^[16]。ADS 存在孕激素受体基因启动子区甲基化相关的表观遗传学变异^[17]。此外,其他一些基因在 ADS 发生及恶变中的生物学功能仍有待确定。目前,ADS 良性病变与恶变之间的分子连续性需要强有力证据加以确证^[2]。亦有研究指出 ADS 恶变与雌激素受体(estrogen receptor, ER)及孕激素受体(progesterone receptor, PR)表达存在相关性。相关研究认为 ER、PR 表达阳性的 ADS 恶变多倾向于低级别病变,ER、PR 表达阴性的 ADS 恶变多倾向于高级别病变^[18-19]。

现有研究提示高雌激素状态是子宫内膜癌等疾病的常见发病机制之一^[20],而 ADS 与子宫肌瘤、子宫内膜癌等雌激素依赖性疾病联系紧密。

有病例回顾性研究发现在子宫内膜癌的大体标本中常伴随 ADS,其中 6.8% 发生了 ADS 恶变,据此有学者提出 ADS 与雌激素依赖的子宫内膜癌 I 型有相似的恶变途径^[21]。有多个 ADS 恶变相关病例报道中患者有激素替代治疗和/或三苯氧胺的应用史。因此 ADS 恶变可能与内源性和外源性雌激素的刺激相关。Puppa 等^[22]曾报道了 1 例无内源性或外源性高雌激素刺激相关的子宫腺肌病恶变病例,但该病例恶变部位邻近伴有

ER 及类固醇生成酶的过度表达的子宫肌瘤病灶,故呈现出高雌激素的微环境,研究者认为局部的高雌激素环境对肿瘤生长有促进作用。

5 子宫腺肌病恶变的治疗与预后

目前 ADS 恶变的治疗方式多为综合治疗,以手术为主,放化疗为辅,其手术范围尚无统一标准。有研究指出其治疗方式可为全面分期手术后辅以铂类为基础的化疗,亦有研究对 ADS 恶变为 I A 期子宫内膜癌者仅行全子宫+双侧附件切除术^[23-25]。由于 ADS 恶变发病率低,目前对其预后的相关研究较少。有研究认为多数 ADS 恶变肌层浸润深度浅,多无淋巴血管间隙浸润及淋巴结转移,预后较好,但仍有待进一步随访观察。

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(上接第 11 页)

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