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·个案报告·

免疫检查点抑制剂治疗BRCA2胚系突变晚期三阴性乳腺癌后超进展一例及文献复习

Hyperprogression of advanced triple-negative breast cancer with BRCA2 germline mutation after immune checkpoint inhibitor treatment: a case report and literature review

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三阴性乳腺癌(triple-negative breast cancer,TNBC)是雌激素受体(estrogen receptor,ER)、孕激素受体(progesterone receptor,PR)和人表皮生长因子受体2(human epidermal growth factor receptor 2,HER2)表达均为阴性的一类乳腺癌,在所有乳腺癌患者中占比为20%~25%[1-3]。尽管有研究报道部分靶向药物可用于晚期TNBC,部分免疫检查点抑制剂(immune checkpoint inhibitor,ICI)已被证实可用于TNBC新辅助化疗及晚期的一线治疗中[4],但化疗仍然是TNBC目前的主要治疗手段,且患者行多线治疗进展后缺乏有效治疗手段。本文报道一例携BRCA2胚系突变晚期TNBC多线治疗进展接受ICI治疗后出现超进展(hyperprogressive disease,HPD)的病例。

1 病例资料

患者为48岁的中年女性,因"发现左乳肿块半年"于2016-12-21行左乳腺癌改良根治术。术后病理:左乳外上象限乳腺浸润性导管癌Ⅱ级伴坏死,病理分期ⅡB期(pT2N1M0);免疫组化:ER(-)、PR(-)、HER2(1+)、Ki67约80%(+)。术后予以6周期"表柔比星+环磷酰胺+多西紫杉醇"方案化疗,末次化疗时间为2017-06-01。患者于2017-10复查胸部CT提示多发肺结节、纵隔淋巴结肿大。2018-01复查CT示肺结节进行性增大,且胸骨出现转移病灶,明确诊断为乳腺癌术后复发转移。患者于2018-01-19至2018-06-28应用"吉西他滨+顺铂"方案化疗6周期,期间肺结节曾有缩小,最佳疗效评价为疾病稳定(SD),无进展生存期(PFS)为6个月。2018-07-25至2018-08-28起行"长春瑞滨+洛铂"方案治疗2周期,疗效评价为PD。2018-09-30至2019-03-05行"白蛋白紫杉醇联合卡铂"方案化疗7周期,期间肺结节缩小,但最佳疗效仍为SD,PFS达5个月。2019-03-16头颅MRI发现新增脑转移,提示肿瘤进展,遂予以全脑放疗,并予以卡培他滨联合贝伐单抗治疗,2周期后肝出现新增病灶,考虑为疾病进展(PD)。2019-06-05予以贝伐单抗(bevacizumab)联合卡瑞利珠单抗(carrelizumab)治疗2周期,200 mg/次。2019-07-05复查胸部CT提示肺部病灶、肝转移病灶快速进展(图1)。2019-07-10行胸壁病灶穿刺活检后病理:低分化腺癌,部分呈肉瘤样变(图2)。

对患者原发肿瘤组织及末次穿刺肿瘤组织进行二代测序(next-generation sequencing,NGS)技术检测,结果显示该患者肿瘤组织中肿瘤突变负荷(tumor mutation burden,TMB)在治疗过程中明显上升,由1 mut/Mb上升至5 mut/Mb,比较治疗前后驱动基因突变为EP300基因突变。

2 讨 论

目前,文献中对ICI使用后HPD的定义有以下几种:(1)肿瘤生长率(tumor growth rate,TGR)在免疫治疗后增加≥2倍[5];(2)治疗失败时间(time to treatment failure,TTF)<2个月,肿瘤负荷增加>50%且免疫治疗后生长进程是之前的2倍以上[6];(3)TGR的变化差值在免疫治疗后首次评价疗效时>50%[7];(4)TTF<2个月,根据RECIST标准可测量病灶最小增加10 mm(与基线比较肿瘤负荷增加≥40%,或增加≥20%的同时出现多个新发病灶)[8]。尽管这些定义略有不同,但是共性上都是指与基线相比的肿瘤快速扩张性生长。

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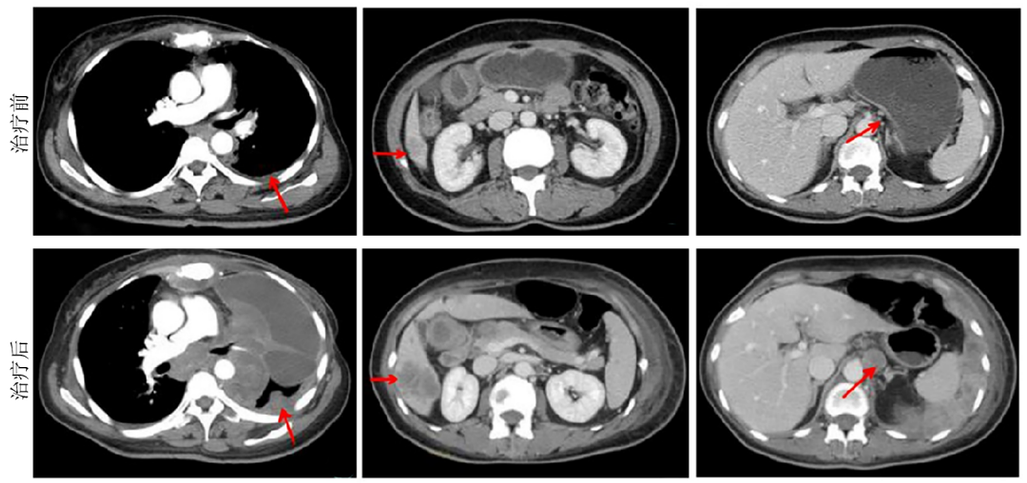

箭头示治疗前后转移病灶的变化

图1 卡瑞利珠单抗治疗前后CT影像比较

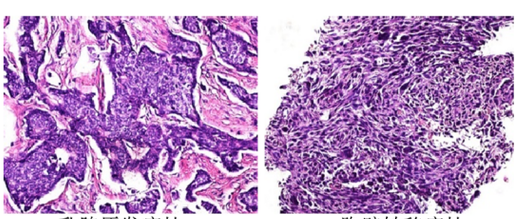

图2 原发肿瘤病灶与胸壁转移灶病理比较（H-E染色，×200）

目前肿瘤学界公认TNBC患者并不能从内分泌治疗或HER2靶向治疗中获益，传统化疗仍是该亚型的主要治疗方式，而且其对化疗较非TNBC更敏感[9-10]。BRCA1/2突变提示同源重组修复缺陷。多项研究[11-14]证实，BRCA1/2胚系突变晚期TNBC在二线及二线以后可考虑聚腺苷酸二磷酸核糖转移酶[poly（ADP-ribose）polymerase，PARP]抑制剂使用。本例患者为携带BRCA2胚系突变的TNBC，辅助化疗结束半年后快速出现骨转移和肺转移。随后，给予患者晚期乳腺癌的解救治疗方案，期间含铂方案化疗曾一度控制病情进展，最长PFS为6个月。然而，多次换线治疗对疾病均控制不佳，且患者由于经济原因未选择PARP抑制剂。在5线治疗失败后，应用卡瑞利珠单抗治疗2周期后发现胸壁及肝转移病灶均快速进展。穿刺活检明确为肿瘤组织，甚至呈肉瘤样变趋势，考虑出现抗PD-1单抗治疗相关的HPD。

本例患者原发病灶的基因检测表明，患者除BRCA2胚系突变外肿瘤组织还存在P53、NF1和RB1基因的驱动突变。既往研究[15-17]表明，P53突变是乳腺癌最常见的基因突变，占比大约在30%~40%，且发生于编码DNA结合域的P53突变与乳腺癌患者的不良预后相关。P53功能缺失可以诱导上皮间质转化（epithelial-mesenchymal transition，EMT）[18-20]。患者同时存在RB1基因的体系突变，该基因与P53同时失活对EMT具有较大的促进作用[21]。RB1缺失可以使细胞绕过致癌基因诱导的细胞衰老从而导致失控的细胞增殖，同时降低上皮型钙黏蛋白表达促进EMT[22]。该患者具有BRCA2胚系突变，在此基础上反复积累了P53、RB1等基因突变后进展为乳腺恶性肿瘤，而且这个肿瘤具有显著的EMT的分子基础。尽管该病例在确诊后经过了积极的辅助治疗，但是患者的肿瘤仍然出现了快速进展，而且对化疗的敏感性有限。NF1是一种编码神经纤维蛋白的肿瘤抑制基因，其可作为RAS-GTP激活的阻遏物，而NF1的缺失则导致RAS激活和MAPK通路的下游激活[23]，拥有NF1胚系突变会使得50岁以下女性罹患乳腺癌风险提高，同时也会增加死亡风险[24-26]。另外，NF1体系突变在肿瘤原发灶中并不常见，一般都是出现在转移癌中[27]，通常认为这是在治疗的选择性压力下导致获得性的基因突变，但是与预后差和高复发风险相关[28]。该患者原发肿瘤即存在该基因的体系突变，可能暗示其最终的不良预后。

EP300编码P300蛋白，属于抑癌基因，而P300缺失的细胞将陷入无节制的增殖和分裂中[29]。EP300在P53/MDM2通路具有重要意义，MDM2是P53的负性调控子，最初被鉴定为致癌蛋白[30]，它是由核转录因子P53激活产生[31]，与P53构成负反馈环路，可以通过连接P53的反式激活功能结构域[32]从而抑制P53介导的反式激活[33]，同时它也可以在连接P53后将其移至细胞质[34]，而在细胞质中P53不能发挥其生物学功能，并且MDM2靶向P53后还可以启动泛素化降解过程[35]。P300作为转录共激活因子也是通过与上述的结构域结合[36-37]，配合P53发挥抑制肿瘤的作用，故P300与MDM2构成竞争性抑制关系。该患

者胸壁转移灶NGS检测结果发现新增EP300突变，该突变是该患者治疗过程中获得的基因突变，将直接导致MDM2表达上调，MDM2可以通过降解转录因子NFATc2抑制T细胞的活化，从而导致对PD-1单抗治疗抵抗，这种免疫耐受的建立可能和HPD相关，因为MDM2同时作为一种肿瘤相关抗原在多种恶性肿瘤中有表达[38]。目前已有临床回顾性研究[6]显示，MDM2扩增的患者在抗PD-1单抗治疗后容易出现HPD，推测该患者携带EP300突变与免疫治疗后疾病快速进展存在关联。

自2016年CHUBACHI等[39]首次报道了使用纳武单抗（nivolumab）治疗非小细胞肺癌过程中出现疾病加速进展的案例以来，临床上使用抗PD-1/PD-L1治疗过程中出现疾病HPD的事件层出不穷，但主要集中在肺癌治疗领域。HPD是免疫治疗领域特有现象还是发生于某些具有特殊临床病理特征的亚组人群目前尚未可知。伴随着免疫治疗越来越多的应用，基因组数据提示MDM2、MDM4和EGFR基因扩增是预测HPD的标志物，但这都是基于回顾性研究并未形成共识，亟需进一步探索出一些生物标志物筛出这类人群。

总之，本文在国内首次报道了多线治疗失败后的TNBC，在使用卡瑞利珠单抗治疗过程中出现疾病加速进展，提示免疫治疗后发生HPD可能与P53、NF1、RB1、EP300基因突变有关，其具体的机制有待深入研究。

[关键词] 三阴性乳腺癌（TNBC）；BRCA2胚系突变；免疫治疗；超进展

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