Introduction/Background Microsatellite instability plays an important role in the development of sporadic endometrial cancer. Mutations in mismatch repair proteins lead to MSI which leads most commonly to somatic hypermethylation and inactivation of MLH1-gene.

Methodology We report a case of endometrioid endometrial adenocarcinoma (EAC) which demonstrated a ‘double hit’ or bi-allelic somatic inactivation of MSH2-gene.

Results A 56 yo nulliparous lady presented with post-menopausal bleeding. Histology of endometrial curettings confirmed grade one EAC, estrogen receptor positive, p53 wild type and MMR deficient. CT-TAP was negative for metastasis. Patient underwent total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. Sentinel lymph node mapping was unsuccessful however intra-operative assessment demonstrated myometrial-invasion <50%, and comprehensive pelvic lymph node dissection was deemed unnecessary. Post-operative histology gave a stage of FIGO 1a, pT1aNxMo, Grade 1 EAC. The was no LVS/cervical stroma/adnexal/parametral involvement. MMR-immunohistochemistry demonstrated loss of MSH2 and MSH6 suggestive of Lynch syndrome (LS), however germline testing failed to identify any abnormality. Further somatic testing identified two independent presumed somatic pathogenic MSH2 mutations. This reduces likelihood of LS and presented an extremely rare case of double somatic mutation of MSH2-gene.

Conclusion MMR gene alterations (hMLH1/hMSH2) play an important role in the development of MSI in sporadic EAC. Most presumed sporadic, MSI-positive EACs are associated with epigenetic silencing of MLH1, via promoter hypermethylation. A smaller fraction have somatic mutations in MSH6, or loss of MSH2 protein expression. Hereditary cancers can also display mutations in MSH2-gene. LS is an autosomal dominant hereditary cancer syndrome which increases cancer risk, most notably colorectal and endometrial. It is caused by germ-line mutations in MMR genes – MSH1/MSH2/MSH6/PMS2 and EPCAM-genes. ~36% of MMR deficient EAC are caused by LS. Here we report a case of EAC demonstrating a ‘double hit’ or bi-allelic somatic inactivation of MSH2-gene highlighting the importance of complete clinical algorithms in these cases.