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ANATOMICAL PATHOLOGY

Mismatch repair deficiency is implicated in carcinoma arising from ovarian teratoma

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Summary

Malignant transformation of benign mature ovarian teratoma can result in a wide spectrum of cancer, including a variety of carcinoma, sarcoma, or melanoma. The role of mismatch repair defects in such malignant transformation is still elusive. In view of current immunotherapy, the role of mismatch repair deficiency can have significant implications on therapeutic strategy. Thus, we aimed to investigate the possible involvement of mismatch repair deficiency in somatic-type carcinoma arising from teratoma. We examined seven cases of malignant transformation of ovarian teratoma to carcinoma from the years 2000–2017. Mismatch repair deficiency was demonstrated in two cases, one of which was a squamous carcinoma and another a sebaceous carcinoma. By immunohistochemistry and molecular studies, we detected mismatch repair protein deficiency, microsatellite instability (MSI) and *MLH1* promoter methylation in the derived carcinoma, but not in the benign teratoma, indicating mismatch repair deficiency was implicated in the process of malignant transformation. Our findings expand the spectrum of genetic alterations which are known to accompany malignant changes in benign teratoma. This finding is also of potential therapeutic significance, as mismatch repair deficient tumours can often be responsive to immune checkpoint blockade because of the high mutational load. In conclusion, we report that a subset of teratoma-derived carcinoma harbours *MLH1* promoter methylation which underlies DNA mismatch repair deficiency, and this subset of patients has the potential to benefit from immunotherapy.

Key words: Teratoma; microsatellite instability; immunotherapy.

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INTRODUCTION

Benign ovarian teratoma is a neoplastic manifestation of pluripotency of abnormal germ cells.[1,2] These tumours give rise to the most unusual clinical scenario where structures of the skin, skin adnexa, as well as structures derived from different germ layers, can be found in the same tumour.[3] Unfortunately, malignant changes can occur in any of these tumour tissues, producing an equally large spectrum of cancers which can encompass many carcinomas,[4] sarcomas,[5] or melanomas,[6] and have salient adverse prognostic implications.[4]

We hypothesised that a hypermutable phenotype due to DNA mismatch repair defects may be present in teratoma which confers its ability to generate such a wide range of aberrations. Microsatellite instability (MSI) is a manifestation of such DNA mismatch repair defects and can play a role in various familial and sporadic cancers.[7] Importantly, because MSI predisposes the tumour to a high genomic mutation load and hence an increased antigen load, it has been recently shown that immunotherapy which enhances T-cell response to tumour antigens, such as immune checkpoint blockade, can be highly effective in mismatch repair deficient cancer, probably regardless of the cancer type.[8] The susceptibility to mismatch repair deficiency can be inherited, such as in the more well-known example of Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC). Muir–Torre syndrome belongs to a subset of this disease, and predisposes the patient to sebaceous carcinoma and various visceral tumours.[9,10] The affected patient has a germline defect in mismatch repair genes on one allele and an inactivating mutation on the other.

We investigated seven cases of somatic-type carcinoma arising from teratoma, and detected mismatch repair deficiency in two of the cases, including one squamous carcinoma and one sebaceous carcinoma. Squamous cell carcinoma is the most common form of malignancy to arise from benign teratoma, while sebaceous carcinoma arising from benign teratoma is exceedingly rare. By immunohistochemical and molecular study, the underlying mechanism of MSI by *MLH1* promoter methylation was demonstrated. The clinical significance and therapeutic implications of these findings are discussed.

MATERIALS AND METHODS

All cases of ovarian teratoma-derived carcinoma diagnosed in the years 2000–2017 in a tertiary referral hospital, with available clinical records and pathological materials were retrieved and reviewed. Immunohistochemical studies were performed with a polymer detection system and the BOND-MAX (Leica, Germany) or Benchmark (Roche, USA) automated immunostainer, using antibodies against the following antigens: PAX-8 (10336-1-AP; 1:300; Proteintech, USA), Adipophilin (Rabbit polyclonal; 1:100; Cell Marque, USA), EMA (M0613; 1:800; Dako, Denmark), MLH1 (554073; 1:150; BD Pharmingen, USA), MSH2 (NA27; 1:100; Calbiochem, USA), MSH6 (610918; 1:500; BD Transduction, USA), and PMS2 (556415; 1:300; BD Pharmingen). Frozen section was performed on formalin fixed tumour tissue for the case of teratoma-derived sebaceous carcinoma and stained for Oil-Red-O. Tumours showing positive staining for all of MLH1, MSH2,

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MSH6, and PMS2 were designated as being mismatch repair proficient; otherwise, the samples were subjected to further molecular analyses.

Molecular analyses

For MSI status analyses, the extracted DNA was amplified by polymerase chain reaction (PCR) at the microsatellite domains using fluorescent-labelled primers. The primers were in accord with the Bethesda panel,[7] and in this study included BAT25, BAT26, BAT40, D2S123, D17S250, and D5S346. The fluorescent-labelled PCR amplicons were loaded on an ABI 310 sequencer, and were subsequently analysed by the GeneMapper software (Applied Biosystems, USA).

For *MLH1* promoter methylation detection, DNA was extracted from the formalin fixed, paraffin embedded (FFPE) specimens, treated by bisulfite conversion (Zymo Research, USA) and subjected to methylation specific PCR of the *MLH1* promoter. Unmethylated DNA from peripheral blood of healthy subjects and methylated control DNA obtained from methylated Jurkat cell line served as negative and positive controls, respectively, for bisulfite conversion and PCR.

RESULTS

Clinical features

Seven women (mean age 56 years; range 28–85 years) were diagnosed to have carcinoma arising from ovarian teratoma in the years 2000–2017 (Table 1). Of these, two had poorly-differentiated squamous cell carcinoma (SCC), four had moderately differentiated SCC, and one had sebaceous carcinoma. Three patients suffered from peritoneal metastases and one had endocervical tumour recurrence. The median progression-free survival was 3.73 months and the median overall survival was 8.47 months. Two patients (Patients 1 and 2) had cancers later shown to be mismatch repair deficient. Patient 1 was an 85-year-old woman with history of an ovarian cyst of static size for more than three decades. She suffered from teratoma-derived SCC presenting with progressive abdominal distention for 6 months and intestinal obstruction for 1 week. Intraoperatively, a large mass occupying the abdomen and pelvis with dense adhesion to the anterior abdominal wall and descending colon was found. Hartmann operation and adhesiolysis were performed. The patient received palliative care, and succumbed to peritoneal metastases 5 months later. Patient 2 was a 45-year-old woman who had good past health and suffered from teratoma-derived sebaceous carcinoma presenting with abdominal distention for several weeks. The initial surgical removal was incomplete due to tumour invasion into the posterior uterus, cervix and the pouch of Douglas. Another operative session with further debulking was performed shortly after, with extensive presence of metastatic tumour noted on the serosal surface of the uterus and bowel, the omentum, and with the tumour involving the small bowel to cause obstruction. The patient later returned to her home country and was lost to follow-up.

Pathological findings

The five teratoma-derived carcinomas later shown to be mismatch repair proficient (Patients 3–7) were SCC, ranging in size from 4.5 to 16 cm. The neighbouring mature teratoma component contained skin and its adnexa ($n = 5$), neuroglial tissue ($n = 3$), smooth muscle ($n = 1$), and columnar epithelium ($n = 1$).

For the mismatch repair deficient tumours, in Patient 1 the ovarian tumour measured 23.5 cm in maximum dimension, and consisted of a cystic component which merged with an infiltrative and solid carcinomatous component. It adhered to the colonic wall and focally perforated into the colonic lumen. Microscopically, the tumour was a squamous cell carcinoma arising from a mature teratoma which contained skin and skin appendages, urothelium, ciliated columnar cell epithelium, smooth muscle, scattered thyroid colloid, osseous, and neuroglial tissue (Fig. 1A–D). The tumour invaded into the colonic submucosa. In Patient 2, the tumour measured 14 cm maximally and contained a prominent solid nodular area with necrosis of 5 cm in greatest dimension, which corresponded to the malignant component; the benign cystic component contained hair, skin and its adnexae, fat, smooth muscle cells and neuroglial tissue, without other immature elements. Microscopically, the carcinomatous component consisted of nests and sheets of cells which exhibited marked nuclear pleomorphism and hyperchromasia, distinct nucleoli, and moderate amount of eosinophilic or clear cytoplasm with frequent mitoses (Fig. 2). Histochemically, the clear cytoplasm of the malignant cells was stained negative for mucin (mucicarmine) and glycogen [periodic acid–Schiff (PAS)]. Lipid stain (oil-red-O) was performed on frozen section of the formalin fixed sample and demonstrated cytoplasmic

Table 1 Seven patients with carcinoma arising from benign ovarian teratoma diagnosed in years 2000–2017

Patient	Age, years	Tumour size, cm[a]	Malignant component	Stage[b]	LVSI	Adjuvant treatment	Survival status	Mode of recurrence	PFS, months	OS, months
Mismatch repair deficient cancers										
1	85	23.5	Poorly differentiated SCC	IIIC	Yes	None	Died	Peritoneal metastasis	3.7	3.93
2	45	14	Sebaceous carcinoma	IIIC	Yes	None	Survived		2.03	2.03
Mismatch repair proficient cancers										
3	69	14	Moderately differentiated SCC	IA	No	ChemoRT	Died	Endocervix recurrence	4.7	17.33
4	28	5	Moderately differentiated SCC	IA	No	None	Survived		69.97	69.97
5	51	10	Moderately differentiated SCC	IC	No	Chemo	Died	Peritoneal metastasis	3.73	8.47
6	54	16	Moderately differentiated SCC	IA	No	None	Died	Peritoneal metastasis	2.9	7.63
7	60	4.5	Poorly differentiated SCC	IA	No	Chemo	Survived		4.5	4.5

All cases involved unilateral ovary.
Chemo, chemotherapy; LVSI, lymphovascular space invasion; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SCC, squamous cell carcinoma.
[a] Largest dimension.
[b] Stage of disease at the time of operation.

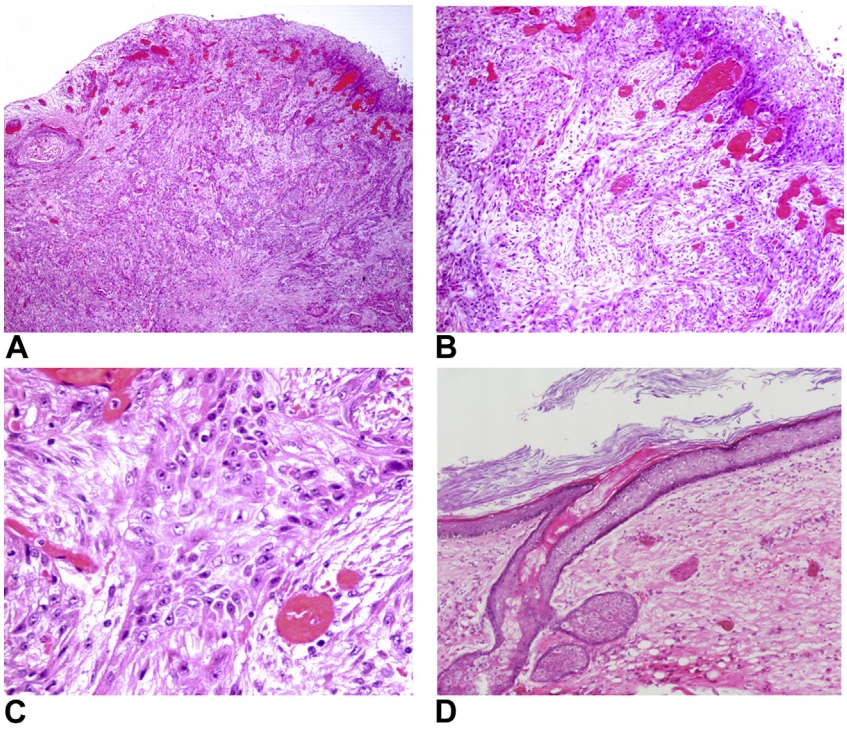

Fig. 1 Morphological and immunohistochemical features of the MSI-implicated teratoma-derived squamous carcinoma. (A) Low power, (B) medium power, (C) high power magnification. Malignant squamous cells with stromal infiltration and intracellular bridges are evident. (D) Benign teratomomatous component adjacent to the squamous carcinoma (low power).

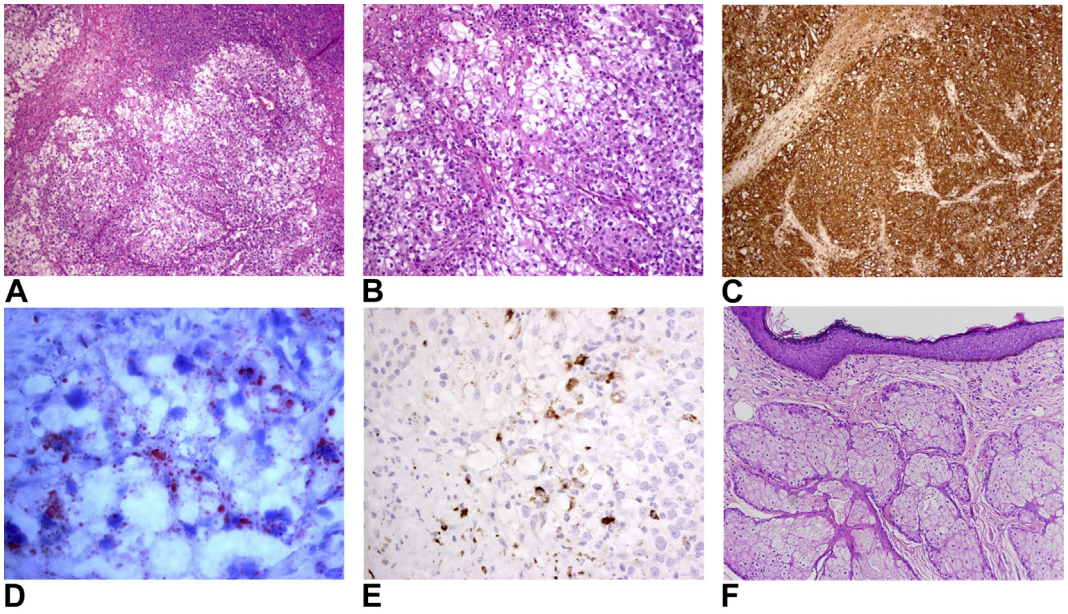

Fig. 2 Morphological and immunohistochemical features of the MSI-implicated teratoma-derived sebaceous carcinoma. (A) Medium power and (B) high power magnification. (C) Tumour cells feature EMA-positive clear cytoplasm (medium power). (D,E) Cytoplasmic lipid which stains for (D) Oil-Red-O and (E) adipophilin, a protein associated with intracellular lipid droplets (high power). (F) Benign teratomomatous component, adjacent to the sebaceous carcinoma.

positivity (Fig. 2D). Adipophilin, an antibody to a lipid droplet-associated protein, was stained focally positive (Fig. 2E). Immunohistochemically, the malignant cells were strongly positive for epithelial membrane antigen (Fig. 2C) and were negative for markers which are used for exclusion of other diagnostic possibilities, such as other malignant germ cell tumours (PLAP, HCG, Oct3/4, AFP), squamous (p40) and adenocarcinoma (CEA). The findings supported the diagnosis of sebaceous carcinoma.

Analyses for mismatch repair deficiency

In patients 3–7, immunohistochemical markers MLH1, MSH2, MSH6 and PMS2 showed preserved staining in both carcinomatous and teratomatous components, indicating there was no mismatch repair protein deficiency. In Patients 1 and 2, mismatch repair protein deficiency was demonstrated in the carcinomatous component, which showed loss of MLH1 and PMS2, while all the markers were retained in the benign teratoma (Fig. 3 and 4).

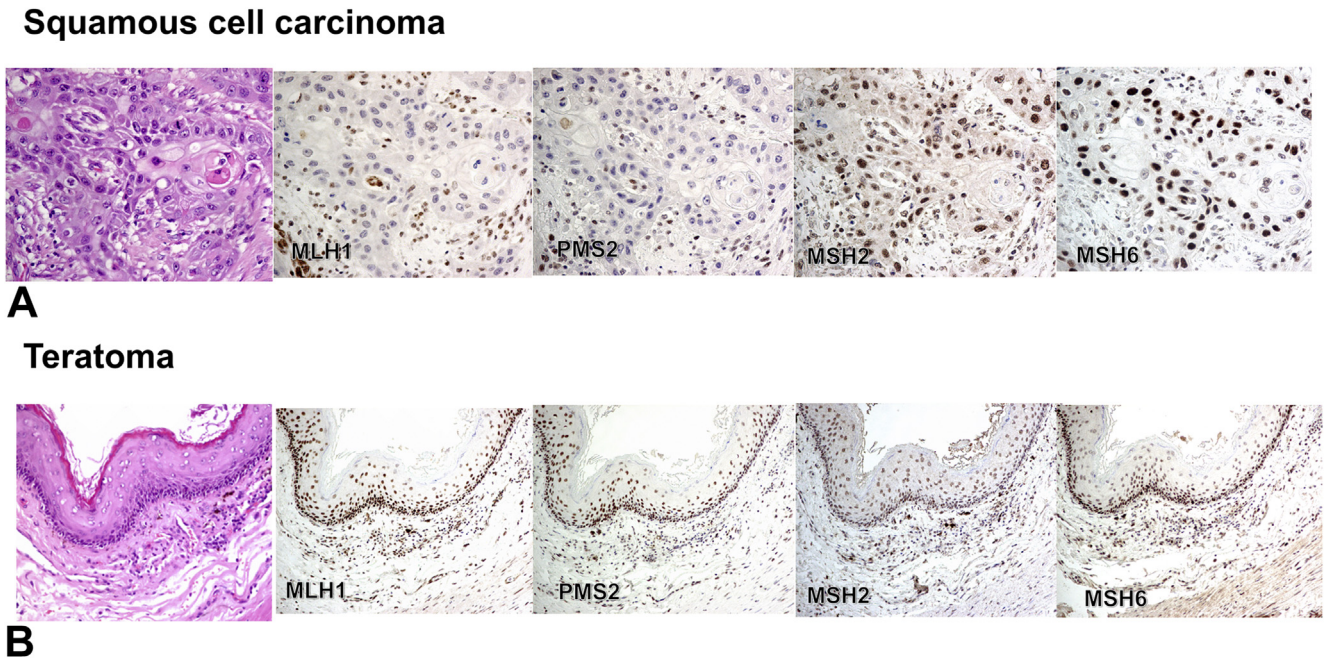

Fig. 3 Immunohistochemical studies of microsatellite instability (MSI) markers. (A) Teratoma-derived squamous cell carcinoma (high power). Two DNA mismatch repair proteins, MLH1 and PMS2, showed loss of staining, while staining for MSH2 and MSH6 was preserved. (B) Skin epithelium in the benign teratoma, showing positive staining for all markers, i.e. negative for MSI (medium power).

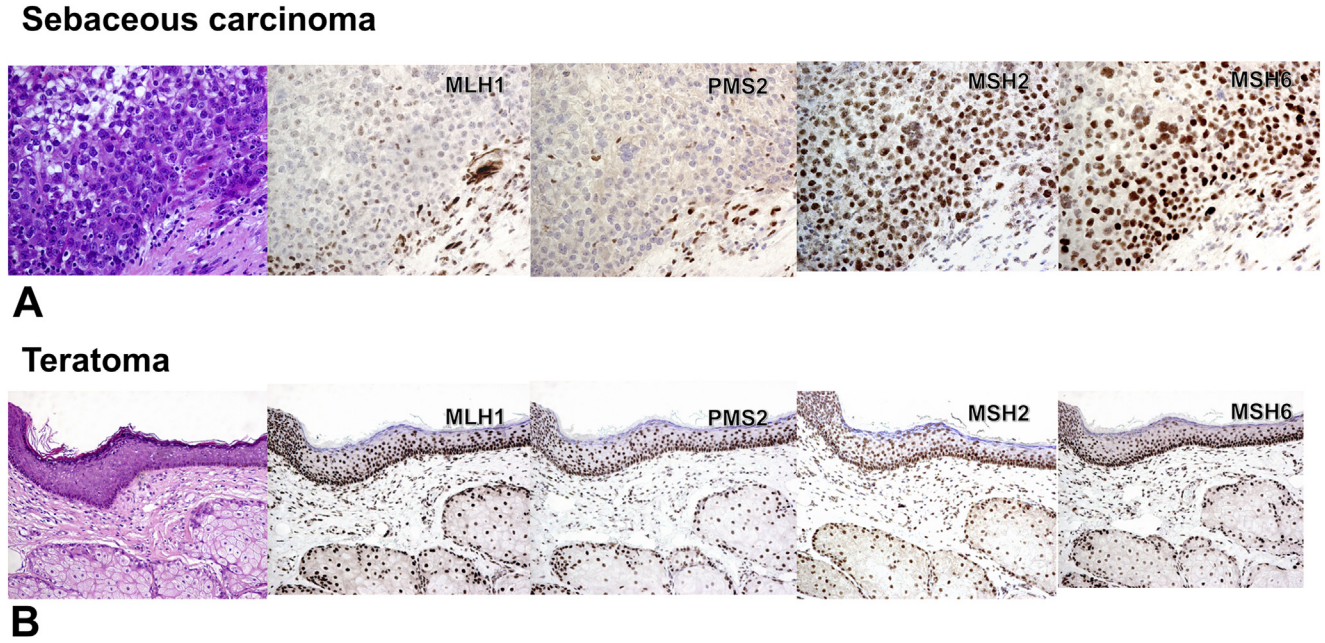

Fig. 4 Immunohistochemical studies of microsatellite instability (MSI) markers. (A) Teratoma-derived sebaceous carcinoma, featuring tumour cells with lipid-containing clear cytoplasm (high power). Two DNA mismatch repair proteins, MLH1 and PMS2, showed loss of staining, while staining for MSH2 and MSH6 was preserved. (B) The benign teratoma, showing positive staining for all markers, i.e., negative for MSI (medium power).

We further applied the Bethesda panel of microsatellite markers on these two patient samples for more definitive proof of MSI (Fig. 5 and 6). Normal fallopian tube tissues from each patient were used as controls. For both cases, at the loci of mononucleotide repeats BAT25, BAT26 and BAT40, alleles with shortened lengths were detected in the carcinoma. As for dinucleotide repeats, the teratoma-derived sebaceous carcinoma (Patient 2) showed alleles of shortened length at the D2S123 and D17S250 loci. Altered alleles of increased length at D5S346 locus of dinucleotide repeats were detected in both cases. At all studied loci, the repeat lengths of the benign teratoma in both cases resembled that of the normal tissue. Because >40% of mononucleotide and dinucleotide repeat loci we evaluated exhibited instability, the findings indicated that the teratoma-derived SCC (Patient 1) and sebaceous carcinoma (Patient 2) had MSI-H phenotype according to the Bethesda criteria.[7,11]

To investigate the underlying mechanism of mismatch repair deficiency in these tumours, we proceeded to perform *MLH1* promoter methylation specific PCR. The state of *MLH1* promoter was studied because silencing of the *MLH1* gene accounts for a large proportion of sporadic MSI-H

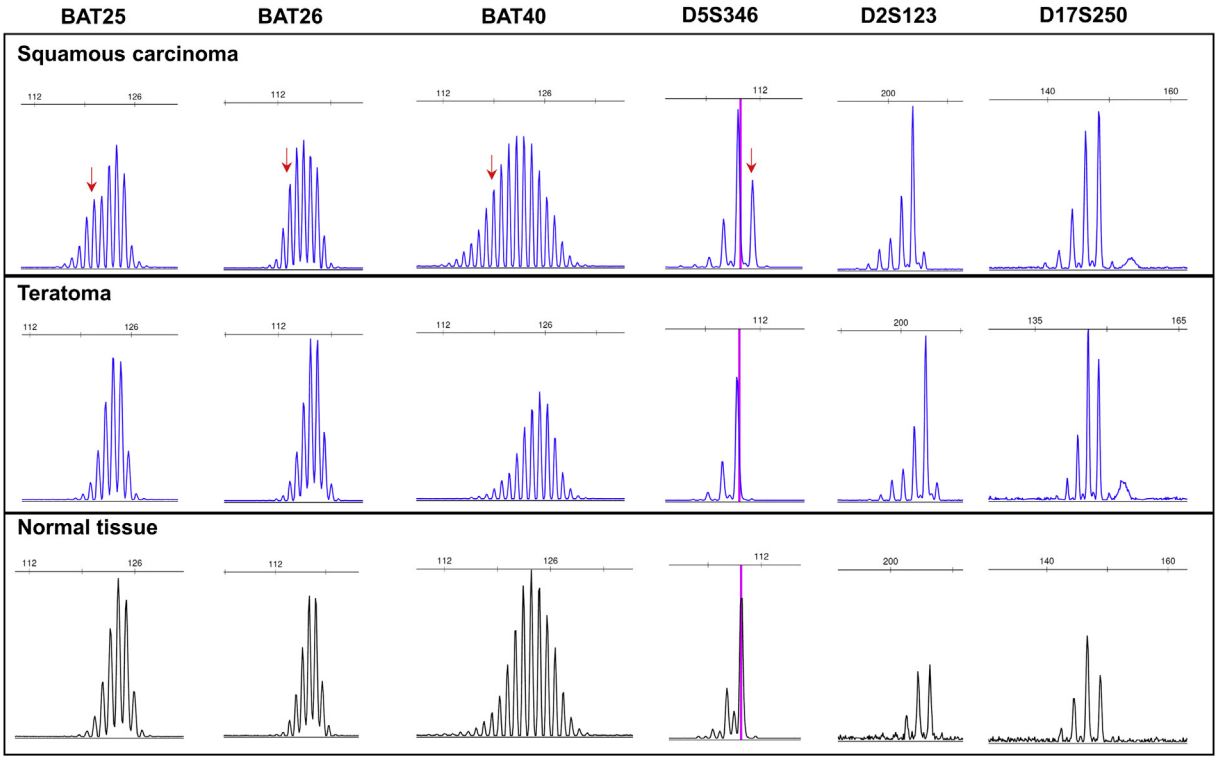

Fig. 5 Electropherograms of PCR-amplified microsatellite markers of squamous carcinoma and the teratoma from which it was derived, with normal fallopian tube tissue as the control. The squamous carcinoma shows shift of allele lengths in microsatellite markers BAT25, BAT26, BAT40 and D5S346 (arrows), indicative of microsatellite instability.

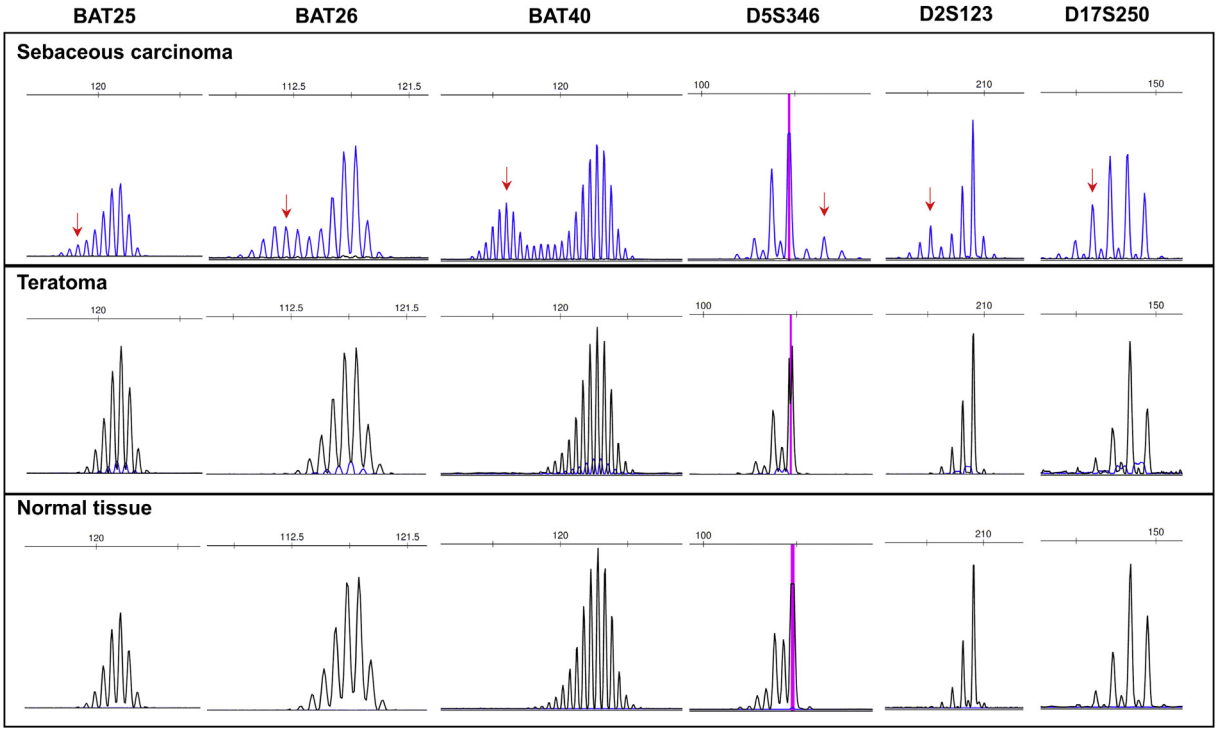

Fig. 6 Electropherograms of PCR-amplified microsatellite markers of sebaceous carcinoma and the teratoma from which it was derived, with normal fallopian tube tissue as the control. The sebaceous carcinoma shows at least 3 bp shorter amplicons in microsatellite markers BAT25, BAT26, BAT40, D2S123 and D17S250, and amplicons of increased length in D5S346 (arrows). These are indicative of altered alleles in all markers, consistent with microsatellite instability.

tumours.[12] The results showed that the *MLH1* promoters were methylated in the carcinomatous component of both Patients 1 and 2 (Fig. 7), and thus accounted for the loss of *MLH1* which was also detected by immunohistochemistry.

DISCUSSION

Malignant transformation of benign teratoma is a rare occurrence, only in 0.17–2% of cases.[4] Previously reported genetic

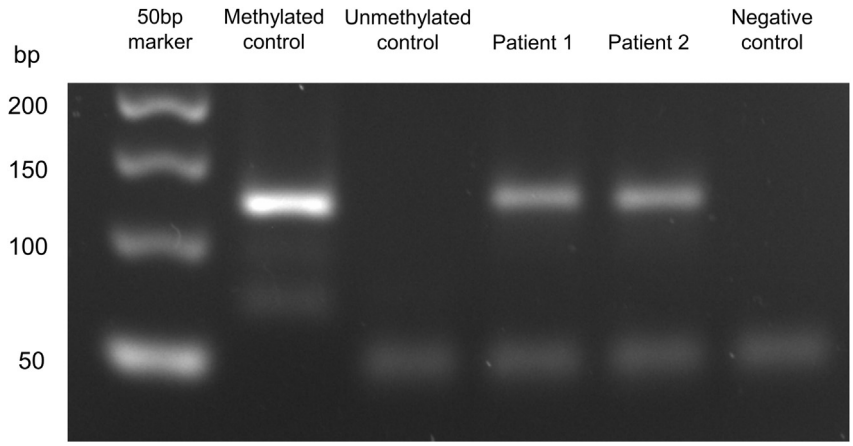

Fig. 7 Gel electrophoresis for MLH1 promoter-methylation specific PCR. The MLH1 promoter-methylated control and promoter-unmethylated control were obtained from Jurkat cell line and peripheral blood of healthy subjects, respectively (see methods). The carcinomatous tissues of Patients 1 and 2 were tested. The negative control contained no DNA template. MLH1 promoter-methylated samples (methylated control and both patient samples) showed an amplicon between 100 and 150 bp, in addition to primer-dimers at the 50 bp region.

aberrations implicated in this process are, for example, *p16, p53* for transformation to squamous cell carcinoma,[13] *KRAS* mutation for struma ovarii to papillary thyroid carcinoma[14] and to intestinal adenocarcinoma.[15] Chromosomal aberrations, such as gain in chromosome,[16] and loss of heterozygosity,[17] are also documented. However, there are scant reports discussing a common mechanism of genetic changes among various types of malignant transformations. The molecular basis underpinning the wide spectrum of malignant manifestations in teratoma remains elusive. We hypothesised that one explanation for the propensity of various oncogenic changes in teratoma may be due to a hypermutable phenotype, a result of DNA mismatch repair defects.

DNA mismatch repair defects can predispose to mutations in the genome, and account for some cases of colorectal cancer, sebaceous carcinoma, endometrial carcinoma, and ovarian endometrioid carcinoma.[7] Very few studies concerned the role of MSI in the pathogenesis of teratoma or its malignant transformation. Faulkner and Friedlander reported genetic instability in four of 19 ovarian immature teratomas, and in a variety of other malignant germ cell tumours.[18] King *et al.* observed MSI in one of three ovarian immature teratomas.[19] Mayer *et al.* performed microsatellite analyses for 100 germ cell tumours, including nine mature teratomas, and failed to observe any MSI-high phenotype in these tumours.[20] None of these series had included teratomas with somatic type malignant transformation.

We detected mismatch repair deficiency in the malignant transformation of teratoma to a squamous cell carcinoma and a sebaceous carcinoma. The latter case is of exceptional interest, because this occurrence is exceedingly rare. Only a small number of case reports have studied this tumour, and its histogenesis is incompletely understood.[21–26] Betta and Cosimi reasoned that it was not a result of sebaceous metaplasia of malignant squamous elements derived from a teratoma,[21] while Ribeiro-Silva *et al.* hypothesised that the sebaceous carcinoma may have arisen from either differentiated sebaceous cells in the mature cystic teratoma or *de novo* from stem cells.[23]

Sebaceous carcinoma may occur sporadically, where mismatch repair deficiency is unusual. Harwood *et al.* noted mismatch repair defect in two of five sporadic sebaceous carcinomas in renal transplant recipients, but none of the four tumours in healthy individuals. The authors reasoned that immunosuppression may have unmasked a hypermutator phenotype.[27] Meanwhile, no evidence of mismatch repair defect was found in 10 sporadic sebaceous carcinoma in the series by Rajan *et al.*,[28] and in 8 sporadic tumours in the series by Entius *et al.*[29] Sebacous carcinoma can also arise in the context of Muir–Torre syndrome, when mismatch repair deficiency is present in the germline. Patients having this syndrome are susceptible to sebaceous carcinoma and visceral cancers affecting the colon, ovary, endometrium, and the urinary system.[30] There is no evidence to support that either patients in this study had underlying Muir–Torre syndrome, because apart from the carcinomatous components in the ovary, they had no history of other visceral malignancy.

In this study, we demonstrated that MSI-H state was present only in the transformed carcinoma but not the benign teratoma. Previously, it was shown that a proportion of teratomas and their derived cancer harboured similar chromosomal amplification and loss of heterozygosity, a finding consistent with their clonal origin.[17] The acquisition of mismatch repair deficiency superimposed on pre-existing molecular aberrations is likely to be critical in the malignant transformation of teratomas, at least in a proportion of cases.[23]

Another importance in identifying mismatch repair deficiency in teratoma-derived carcinoma lies in its potential therapeutic implications. Some MSI-implicated cancers contain significantly more tumour-infiltrating lymphocytes, probably because of high mutation load and expression of novel aberrant antigens.[31,32] Unfortunately, tumours can evolve an adaptive immune resistance mechanism and up-regulate PD-L1, a ligand that when bound to PD-1 receptors on T-cells can lead to T-cell inactivation.[33] In a seminal study in 2015, PD-1 receptor blockade was shown to be more effective in mismatch repair deficient colorectal, endometrial, small bowel, bile duct and gastric cancer, with an objective response rate of 71%, versus 0% in mismatch repair proficient colorectal cancer.[8] The authors found 24 times more somatic mutations in the former cancer genome than the latter. The data led to the conclusion that PD-1 blockade could be ‘an approach for the treatment of a specific class of tumours that was based solely on genetic status

(i.e., presence or absence of mismatch repair defects), without regard to the underlying tumour type'.[8] Teratoma-derived carcinoma can be a rapidly fatal disease, with widespread peritoneal metastasis occurring in three of seven patients in our cohort. The finding of mismatch repair deficiency in teratoma-derived carcinoma is an important observation which can potentially translate to therapeutic susceptibility. Testing for mismatch repair deficiency in teratoma-derived carcinomas may be important in the future.

We are aware that this study on this rare form of carcinogenesis has several limitations. The number of included samples is small. The question whether teratoma has a propensity to develop mismatch repair deficiency remains unanswered. Although our line of thought is that mismatch repair deficiency likely plays a driving role in the malignant transformation, it is necessary to identify the genes which are mutated due to MSI, probably by means of next generation genome-wide sequencing. The number of genes susceptible to mutation as a result of MSI is expected to be high, and the role of each gene can be difficult to elucidate. Needless to say, even if such efforts are undertaken, the morphological heterogeneity of benign teratoma and the spectral complexity of malignancy to which it can give rise are major complications to sample inclusion and data analyses.

This study provides unique evidence that mismatch repair deficiency may be implicated in malignant transformation of benign teratoma, and the recent finding that mismatch repair deficiency can have a therapeutic implication, especially in immunotherapy, is important to be further explored.

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