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CORRELATION OF MISMATCH REPAIR DEFICIENCY WITH CLINICOPATHOLOGICAL PARAMETERS IN ENDOMETRIAL CARCINOMA

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ABSTRACT

Objective: To estimate the incidence of mismatch repair deficiency in endometrial carcinoma and to refine its association with clinic-pathological parameters, in view of its emerging role in prognostication and therapeutic decision making.

Study design: This cross-sectional study was conducted on 80 histologically proven cases of endometrial carcinoma over a period of 18 months in a tertiary care centre. Representative tumour sections were immunohistochemically analysed for expression of key mismatch repair proteins. Nuclear expression loss in tumour cells was taken as an indication of deficiency. Associations were evaluated against clinical data, such as years, menopausal category and presenting symptoms, and histopathological data, such as tumour type, grade and stage.

Results: Mismatch repair deficiency was detected in 28.7% of patients. The commonest pattern of concomitant loss of two proteins, mainly in tumours of endometrioid histology. Tumours that were deficient were statistically significantly associated with higher tumour grade and increased depth of myometrial invasion. However, no significant association was found with patient age, menopausal status or tumour stage. The results indicate a discrete subset of tumours with specific biological behaviour.

Conclusions: A considerable proportion of endometrial carcinomas harbour mismatch repair deficiency. Routine immunohistochemical assessment may be an inexpensive screening tool to identify that subset of patients who would benefit from further molecular testing, genetic counselling and targeted therapeutic approaches including immunotherapy.

KEYWORDS: Endometrial Carcinoma; Mismatch Repair Deficiency; Immunohistochemistry; Clinicopathological Parameters; Myometrial Invasion.

1. INTRODUCTION

Endometrial carcinoma is one of the most common gynaecological malignancies in the world and constitutes a significant health burden in women, particularly in the postmenopausal age group [1]. Its incidence is rising rapidly, related to longer life expectancy, obesity and changes in reproductive patterns [2]. Traditionally, endometrial carcinoma has been classified into distinct subtypes based on histopathological features; however, this entity does not adequately reflect the biological heterogeneity and different clinical outcomes seen in patients [3]. Recent advances in molecular pathology have changed our understanding of endometrial carcinoma and the role of genetic and molecular changes in the development and progression of this tumour [4]. Mismatch repair deficiency has become one of these key molecular pathways. The mismatch repair system is crucial for the maintenance of genomic stability by correcting errors that occur during DNA replication [5]. Defects in this system result in accumulation of mutations especially in the microsatellite regions leading to micro uncertainty and contributing to carcinogenesis [6]. Mismatch repair deficiency in endometrial carcinoma is associated with specific histological subtypes and tumour grade, and unique clinico-pathological features [7]. Its clinical significance is of great importance. One of the most important aspects is its association with Lynch syndrome, a hereditary malignance predilection disorder due to DNAe mutations in mismatch repair genes [8]. Patients with Lynch syndrome have an increased lifetime risk of endometrial carcinoma, often at a younger age, and other cancers such as colorectal cancer [8,9]. Mismatch repair deficiency in tumour tissue can therefore be used as a first screen for Lynch syndrome, allowing timely genetic counselling and surveillance of affected individuals and their families8. Deficiency of mismatch repair has gained prominence in the context of therapeutic decision-making, beyond its role in the detection of hereditary cancer. Cancers with mismatch repair deficiency have a high mutational burden, which makes them more immunogenic and more susceptible to immune checkpoint inhibitors [10]. Thus, the evaluation of mismatch repair status is becoming more and more relevant in the management of personalised treatment strategies, particularly in advanced or recurrent disease.

Its clinical importance notwithstanding, mismatch repair status is not routinely assessed in all healthcare settings [11]. Test availability may be limited in many centres due to costs, infrastructure or lack of awareness of its clinical utility, especially in resource-poor settings. There is considerable variation in the reported prevalence of mismatch repair deficiency and its association with clinicopathological parameters across different populations and study settings [12]. This underscores the need for country-level data to better understand its distribution and implications. In view of this, the present study aims to evaluate the prevalence of mismatch repair deficiency in endometrial carcinoma and to analyse its association with various clinicopathological features in tertiary care setting. The study aims to add to the existing literature and emphasise the necessity of incorporating mismatch repair testing into routine diagnostic and management pathways.

2. MATERIALS AND METHODS

Study design and setting

This was a hospital-based cross-sectional study conducted in the Department of Pathology of a tertiary care centre over a period of 18 months.

Study population and sample size

The study included 80 cases of histopathologically confirmed endometrial carcinoma. Cases were selected consecutively from hysterectomy specimens received during the study period.

Inclusion criteria

- Histologically confirmed cases of endometrial carcinoma
- Availability of adequate formalin-fixed, paraffin-embedded tissue blocks
- Complete clinical and pathological data

Exclusion criteria

- Inadequate or poorly preserved tissue samples
- Cases with prior chemotherapy or radiotherapy
- Recurrent tumours

Data collection

Medical specifics including age, menopausal status, presenting complaints and relevant past were obtained from medical records. Histopathological parameters such as tumour type, grade, depth of myometrial invasion and stage were recorded from pathology reports.

Histopathological evaluation

All haematoxylin and eosin-stained slides were reviewed to confirm the diagnosis and classify tumours according to standard histopathological criteria. Tumours were evaluated based on architectural and nuclear features using the FIGO (International Federation of Gynaecology and Obstetrics) grading system.13

Immunohistochemistry

Immunohistochemical analysis was performed on representative tumour sections using Ab against mismatch repair proteins. Sections of 3-4 μm thickness were prepared from paraffin blocks, mounted on coated slides and subjected to antigen retrieval.

Primary antibodies against mismatch repair proteins MLH1, PMS2, MSH2 and MSH6 were applied,11 followed by incubation with secondary detection systems. Appropriate positive and negative controls were included in each run.

Nuclear staining in tumour cells was assessed. Intact nuclear staining was considered indicative of proficient mismatch repair status, whereas complete loss of nuclear staining in tumour cells, with retained staining in surrounding stromal or inflammatory cells, was interpreted as mismatch repair deficiency.14

Outcome measures

The chief outcome was the prevalence of mismatch repair deficiency in endometrial carcinoma. Secondary outcomes included its involvement with clinicopathological constraints such as tumorgrowth type, grade, stage and patient demographics.

Statistical analysis

Data were entered and analysed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages. Associations between mismatch repair status and clinic-pathological parameters were assessed using the chi-square test. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations
The study was performed according to the ethical standards of the institution. Prior to initiation of the study, approval was obtained from the Institutional Ethics Committee. Patient confidentiality was preserved and no identifiable patient information was shared.

3. RESULTS

Baseline clinicodemographic characteristics
The study included a total of 80 cases of endometrial carcinoma. Patients' age ranged from 38 to 75 years with the mean age of 56.4 ± 9.2 years. The majority of patients (60%) were post-menopausal at diagnosis. The most common presenting complaint was abnormal uterine bleeding.

Histopathological characteristics
The most common histologic subtype was endometrioid carcinoma (72%), with the remaining 28% being non-endometrioid variants. The tumour grading showed that 35% of the cases were low grade and 65% were high grade. Deep myometrial invasion was present in 42% of the cases. The results are summarised in Table 1.

Table 1: Clinicodemographic and Histopathological Characteristics (n = 80)

Variable	Category	Number (n)	Percentage (%)
Age (years)	<50	18	22.5
	≥50	62	77.5
Menopausal status	Premenopausal	32	40.0
	Postmenopausal	48	60.0
Presenting complaint	Abnormal uterine bleeding	58	72.5
	Others	22	27.5
Histological type	Endometrioid	58	72.5
	Non-endometrioid	22	27.5
Tumour grade	Low grade	28	35.0
	High grade	52	65.0
Myometrial invasion	<50%	46	57.5
	≥50%	34	42.5
Tumour stage	Stage I-II	50	62.5
	Stage III-IV	30	37.5

Prevalence of mismatch repair deficiency
Of 80 cases, 23 cases were identified with mismatch repair deficiency, prevalence of 28.7%. In the remaining 57 cases (71.3%), all mismatch repair proteins were expressed intact.

Patterns of protein expression loss
In mismatch repair-deficient tumours, a prevalent pattern noted was the simultaneous loss of two proteins, observed in 65% of deficient instances. Loss of the other pair of proteins was found in 22% and loss of a single protein alone in 13%. Such a distribution suggests the dominance of coordinated protein loss over isolated deficiencies.

Association with clinicopathological parameters

Mismatch repair deficiency showed a statistically significant association with tumour grade. A higher proportion of deficient tumours were observed in the high-grade category compared to low-grade tumours ($p = 0.03$).

A significant association was also noted with histological subtype, with mismatch repair deficiency being more frequently observed in endometrioid carcinomas compared to non-endometrioid variants ($p = 0.01$).

Although a higher proportion of deficient tumours demonstrated deep myometrial invasion, this association did not reach statistical significance ($p = 0.08$).

No statistically significant association was found between mismatch repair status and patient age ($p = 0.45$), menopausal status ($p = 0.39$), or tumour stage ($p = 0.52$).

Table 2: Association of Mismatch Repair Status with Clinicopathological Parameters

Variable	Category	MMR Deficient (n=23)	MMR Proficient (n=57)	χ^2 value	p-value
Age (years)	<50	6	12	0.04	0.45
	≥50	17	45		
Menopausal status	Premenopausal	10	22	0.02	0.39
	Postmenopausal	13	35		
Histological type	Endometrioid	20	38	2.44	**0.01**
	Non-endometrioid	3	19		
Tumour grade	Low grade	4	24	3.38	**0.03**
	High grade	19	33		
Myometrial invasion	<50%	10	36	1.85	0.08
	≥50%	13	21		
Tumour stage	Stage I-II	13	37	0.02	0.52
	Stage III-IV	10	20		

Representative immunohistochemical staining patterns demonstrating intact and loss of nuclear expression of mismatch repair proteins are shown in Figure 1. Tumour cells exhibiting loss of expression showed absence of nuclear staining with retained staining in surrounding stromal cells, serving as an internal control.

Figure 1. Immunohistochemical staining patterns of mismatch repair proteins

Legend:

(A) Intact nuclear expression in tumour cells (proficient)

(B) Loss of nuclear expression in tumour cells with retained stromal staining (deficient)

(C) Example of dual protein loss pattern

(D) High-grade tumour showing loss of expression

Microscopic images showing immunohistochemical staining of tumour tissue with preserved nuclear staining in some panels and complete loss of staining in tumour cells in others, with retained staining in non-tumour cells.

4. DISCUSSION

The growing emphasis on molecular characterisation in endometrial carcinoma reflects a broader shift in oncological practice towards precision medicine. [4] In this evolving landscape, mismatch repair deficiency is a clinically relevant alteration that bridges histopathological assessment and prognostic/therapeutic decisions5. Its occurrence and associations in different population groups need to be evaluated to improve its integration into routine clinical settings.

In the current study, 28.7% of the endometrial carcinomas were mismatch repair deficiency, which means that almost one-third of the tumours have a deficiency in the DNA repair pathway. This is in line with previously reported rates in the literature, which are usually in the range of 20% to 35% [5]. This agreement improves the reproducibility of these results in different clinical settings and strengthens the reliability of immunohistochemistry as a screening method for mismatch repair status. The observed prevalence underscores the clinical importance of routine testing, particularly in settings where molecular techniques may not be readily available.

One of the key findings in this study was the strong association between mismatch repair deficiency and endometrioid histology subtype. This is consistent with the well documented evidence that alterations in mismatch repair are more common in endometrioid carcinomas [8]. years ago The epigenetic mechanisms, in particular promoter methylation leading to silencing of mismatch repair genes, are thought to be the biological basis for this association.Fifteen. This results in the accumulation of replication errors and microsatellite instability allowing tumorigenesis [6,16]. The lower prevalence of mismatch repair deficiency in non-endometrioid tumours emphasises the molecular heterogeneity of endometrial carcinoma and supports the need for subtype-specific assessment [17].

The present study also demonstrated a significant association from a statistical standpoin between mismatch repair deficiency and higher tumour grade. This advocates that cancerious growth with impaired DNA repair

mechanisms may exhibit more aggressive histological features, potentially due to increased genomic instability and accumulation of oncogenic mutations. [18] While former studies have reported variable associations between mismatch repair status and tumour grade, the verdicts of the prevailing study lend support to the hypothesis that mismatch repair deficiency may be linked to adverse pathological characteristics. [13,19] This has important consequences for risk stratification and may influence clinical decision-making in the future.

With respect to myometrial invasion, a higher proportion of mismatch repair-deficient tumours exhibited deeper invasion; however, this overtone did not influence statistical significance. Similarly, no statistically meaningful correlations were perceived between mismatch repair status and patient age, menopausal status or tumour stage. These discoveries are constant with several prior studies that have reported inconsistent or weak correlations between mismatch repair deficiency and clinicodemographic parameters. [12,20] The lack of significant association in these variables may be attributed to differences in sample size, population characteristics and study design. It also suggests that mismatch repair deficiency may represent an independent molecular feature rather than one that is strongly linked to traditional clinical parameters.

From a distant outlook, the detection of mismatch repair deficiency has multiple important implications. The most noteworthy applications is in the screening for Lynch syndrome, an inherited cancer predisposition disorder associated with germline mutations in mismatch repair genes. [21] Tumour-based immunohistochemical assessment serves as an effective initial screening method to identify patients who may benefit from further genetic evaluation. [22] Early diagnosis of Lynch syndrome impacts the management of the index case and has implications for at-risk relatives, facilitating targeted surveillance and prevention [9].

Beyond its role in hereditary cancer diagnosis, mismatch repair deficiency has emerged as a diagnostic biomarker for immunotherapy response [23]. Tumours with deficient mismatch repair are characterised by a high mutational load that leads to the generation of neoantigens, increasing tumour immunogenicity [11,24]. This biological feature may explain their better sensitivity to immune checkpoint inhibitors. Therefore, the assessment of mismatch repair status is becoming increasingly important to guide treatment decisions, especially in advanced or recurrent endometrial carcinoma [9]. These findings further support the need for the inclusion of mismatch repair testing in routine diagnostic workup to guide personalised therapeutic approaches.

Another key question is whether mismatch repair testing can be integrated into routine practice. Immunohistochemistry is a cheap, readily available and relatively simple method for assessing mismatch repair status and is therefore particularly suitable for resource-limited settings [25]. Twenty-five years ago The practical usefulness of this technique in the present study and its value as a screening tool are emphasised. Wider use of such tests may promote the uptake of advanced molecular diagnostics into routine clinical practice, particularly in areas where access to more sophisticated techniques is limited.

The present study has its merits including systematic evaluation of mismatch repair status by immunohistochemistry and its correlation with different clinicopathological parameters. When staining patterns are interpreted using clearly defined norms, results are more consistent. The study also gives data specific to the region, which is important given the variability across different populations.

There are some limitations to be acknowledged though. The study was performed in a single tertiary care centre with a relatively small sample size which may affect the generalisability of the findings. Furthermore, molecular confirmation of microsatellite instability by the polymerase chain reaction technique was not performed. This could have added further validation of the immunohistochemical findings. Lack of follow-up data does not allow evaluation of survival outcomes and limits evaluation of the prognostic importance of mismatch repair deficiency. Additional research with larger cohorts, multicentric data and outcome analysis would be useful to clarify the role of mismatch repair deficiency in endometrial carcinoma.

We demonstrate here that a notable proportion of endometrial carcinoma shows mismatch repair deficiency and that this is significantly associated with certain pathological features, especially tumour grade and histological subtype. These results highlight the importance of including mismatch repair assessment in routine diagnostics. This integration may improve risk stratification, allow identification of patients with Lynch syndrome and allow implementation of personalised therapeutic strategies, ultimately improving patient outcomes.

5. CONCLUSION

Deficiency in mismatch repair was present in a significant proportion of cases of endometrial carcinoma in this study and correlated clearly with tumour grade and histological subtype. These results highlight its importance as a key molecular marker for the evaluation of endometrial carcinoma. Immunohistochemical evaluation of mismatch repair status is a practical and cost-effective tool for routine screening, particularly in resource-limited settings. Its recognition has major implications for the identification of hereditary cancer syndromes and for the guidance of personalised therapeutic strategies including immunotherapy. Incorporation of mismatch repair testing in standard diagnostic protocols may enhance risk stratification and patient management.

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