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Research Article

PROGNOSTIC SIGNIFICANCE OF DISSEMINATED TUMOR CELLS IN THE BONE MARROW OF PATIENTS WITH OVARIAN CANCER

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ABSTRACT

Background: Ovarian carcinoma is associated with high mortality due to late presentation and early systemic dissemination. Disseminated tumour cells (DTCs) in bone marrow represent occult haematogenous spread and may have prognostic significance.

Aim: To detect disseminated tumour cells in the bone marrow of patients with ovarian carcinoma and to evaluate their association with clinicopathological parameters.

Materials and Methods: This prospective observational study included 52 patients with histopathologically confirmed ovarian carcinoma without radiological evidence of distant metastasis. Surgically resected specimens were assessed for tumour characteristics and lymph node status. Bone marrow aspiration was performed from the bilateral posterior iliac crests, and smears were evaluated using cytomorphological criteria. Cases positive or suspicious for DTCs underwent pan-cytokeratin immunostaining. Statistical analysis was carried out using the chi-square test, and a p-value <0.05 was considered statistically significant.

Results: Disseminated tumour cells were identified in 15.38% of bone marrow smears, while cytokeratin positivity was observed in 11.54% of cases. No significant association was found between DTC positivity and age, menopausal status, tumour stage, lymph node status, histological subtype, or TNM stage ($p>0.05$). A statistically significant association was observed between vascular invasion and DTC positivity ($p=0.01$). All cytokeratin-positive cases demonstrated DTC

positivity, indicating a strong correlation.

Conclusion: Bone marrow detection of disseminated tumour cells indicates early systemic spread in ovarian carcinoma and may have prognostic relevance, particularly in cases with vascular invasion.

Keywords

Ovarian Neoplasms; Disseminated Tumor Cells; Bone Marrow; Cytokeratin; Neoplasm Metastasis; Vascular Invasion

INTRODUCTION

Ovarian cancer is the second most common gynaecological malignancy worldwide and represents the fifth leading cause of cancer-related mortality among women in developed countries. It is the fifth most common malignancy among women globally, accounting for approximately 4% of all female cancers [1].

In India, the age-standardized incidence rate (ASR) of ovarian carcinoma ranges from 0.9 to 8.4 per 100,000 women per year, with the highest incidence observed in the 55–64-year age group. The estimated lifetime risk of developing ovarian cancer is approximately 1 in 75 women [2].

Several risk factors have been implicated in ovarian carcinoma, including advancing age, hormonal influences, reproductive factors such as menopause and hormone replacement therapy, positive family history, genetic susceptibility, and environmental and lifestyle factors [3]. The hypotheses of “incessant ovulation” and gonadotrophin stimulation propose that repeated ovulatory trauma and sustained hormonal stimulation contribute to malignant transformation of the ovarian epithelium [4].

Although the majority of ovarian cancers are sporadic, approximately 5–10% are hereditary, predominantly associated with BRCA1 and BRCA2 tumour suppressor gene mutations, accounting for 10–15% of ovarian carcinomas [5]. In addition, gynaecological conditions such as nulliparity, polycystic ovarian disease, endometriosis, and pelvic inflammatory disease have been associated with an increased risk of ovarian cancer [6].

The ovary’s complex anatomy and cyclical physiological changes from puberty to menopause give rise to diverse cell types capable of malignant transformation. Consequently, ovarian tumours exhibit a wide spectrum of histopathological patterns. According to the World Health Organization (WHO) classification, epithelial ovarian tumours are the most common and possess the greatest malignant potential [7].

Despite advances in diagnostic modalities such as ultrasonography and serum CA-125 estimation, ovarian cancer is frequently diagnosed at an advanced stage due to its asymptomatic early course and continues to have the highest mortality among gynaecological malignancies [8]. Although initial response to cytoreductive surgery and chemotherapy is generally favourable, more than half of patients experience

relapse, and distant metastasis remains a major cause of mortality [9].

The presence of circulating and disseminated tumour cells (DTCs) in the bone marrow represents occult haematogenous spread and has been demonstrated in epithelial malignancies, including ovarian carcinoma [10]. Disseminated tumour cells have been detected in 30–50% of patients with primary ovarian cancer, including early-stage disease, suggesting their potential role as a prognostic marker for disease recurrence and progression [11,12].

AIMS AND OBJECTIVES

1. To evaluate patients with ovarian carcinoma for the presence of disseminated tumour cells in bone marrow.
2. To assess the association between disseminated tumour cells and clinicopathological parameters, including tumour stage and pathological characteristics.

MATERIALS AND METHODS

This cross-sectional study was conducted at Tertiary care Center in Tamilnadu over a period of one year. A total of 52 patients with histopathologically confirmed ovarian carcinoma without radiological evidence of bony or distant metastasis, irrespective of lymphatic spread, were included in the study, while cases of carcinoma in situ, secondary malignancy, prior or ongoing chemotherapy or radiotherapy, and history of other malignancies were excluded. Surgically resected specimens were evaluated for tumour size, extent, lymph node status, histological type, and grade. Bone marrow aspiration was performed from the bilateral posterior iliac crests under local anaesthesia using strict aseptic precautions, and smears were fixed in methanol and stained with Leishman stain. Disseminated tumour cells were identified based on established cytological criteria, including cell size, cytoplasmic borders, nuclear features, and hyperchromasia, and cases were categorized as DTC-positive or DTC-negative; positive or suspicious smears were further evaluated using pan-cytokeratin immunostaining. Data were tabulated and analysed using the chi-square test**,** with ap-value < 0.05 considered statistically significant. The study was conducted following approval from the Institutional Ethics Committee**,** and written informed consent was obtained from all patients.

RESULTS

A total of 52 patients with histologically confirmed ovarian carcinoma were included in the study.

Demographic characteristics

Patient age ranged from 35 to 74 years, with the majority in the 45–54 years and 55–64 years age groups (36.54% each). Postmenopausal women constituted 57.69% (n = 30) of the cohort, while 42.31% (n = 22) were premenopausal. [Table 1, & 2]

Tumour characteristics

T3a was the most frequent tumour stage (30.77%), followed by T1a and T2a

(21.15% each). T2b accounted for 11.54%, T3b for 9.62%, and T1b was least common (5.77%). All patients had lymph node metastasis, with N1a observed in 55.77% and N1b in 44.23%. [Table 3]

Histopathologically, serous carcinoma predominated (63.46%), followed by mucinous (26.92%) and endometrioid carcinoma (9.62%). All cases were classified as Stage III disease, predominantly Stage IIIA1 (59.62%), followed by Stage IIIA2 (30.77%) and Stage IIIB (9.62%).[Table 4 & 5]

Vascular invasion

Vascular invasion was present in 46.15% (n = 24) of patients and absent in 53.85% (n = 28). [Table 6]

Detection of disseminated tumour cells

DTCs in bone marrow smears were detected in 15.38% (n = 8) of patients. Cytokeratin immunostaining identified disseminated epithelial tumour cells in 11.54% (n = 6) of cases.[Table 7& 8]

Association of DTCs with clinicopathological parameters

No significant association was observed between DTC positivity and age, menopausal status, tumour stage, lymph node status, histological subtype, or TNM stage ($p > 0.05$ for all).A statistically significant association was observed between vascular invasion and DTC positivity (χ^2, df = 1; $p = 0.01$).A highly significant association was noted between cytokeratin positivity and DTC detection (χ^2, df = 1; $p = 0.01$), with all cytokeratin-positive cases demonstrating DTC positivity. [Table 9,10,11]

Table: 1 Age distribution among study population (n=52)

Age group (years)	Frequency	Percentage
35–44	10	19.23
45–54	19	36.54
55–64	19	36.54
65–74	4	7.69
Total	52	100

Table: 2 Distribution of menopausal status

Menopausal status	Frequency	Percentage
Postmenopausal	30	57.69
Premenopausal	22	42.31
Total	52	100

Postmenopausal women constituted the majority of ovarian carcinoma cases.

Table: 3 Distribution of tumour staging

Tumour stage	Frequency	Percentage
T1a	11	21.15
T1b	3	5.77
T2a	11	21.15
T2b	6	11.54
T3a	16	30.77
T3b	5	9.62
Total	52	100

Table: 4 Distribution of lymph node status

Lymph node status	Frequency	Percentage
N1a	29	55.77
N1b	23	44.23
Total	52	100

Table: 5 Distribution of histopathological subtype

Histological subtype	Frequency	Percentage
Endometrioid	5	9.62
Mucinous	14	26.92
Serous	33	63.46
Total	52	100

Table: 6 Distribution of TNM staging

TNM stage	Frequency	Percentage
IIIA1	31	59.62
IIIA2	16	30.77
IIIB	5	9.62
Total	52	100

Table: 7 Distribution of vascular invasion

Vascular invasion	Frequency	Percentage
Absent	28	53.85
Present	24	46.15
Total	52	100

Table: 8 Distribution of disseminated tumour cells in bone marrow smears

DTC status	Frequency	Percentage
Negative	44	84.62
Positive	8	15.38
Total	52	100

Table: 9 Detection of disseminated epithelial tumour cells by cytokeratin staining

Cytokeratin status	Frequency	Percentage
Negative	46	88.46
Positive	6	11.54
Total	52	100

Table: 10 Association between vascular invasion and disseminated tumour cells

Vascular invasion	DTC Negative	DTC Positive	Total
Absent	27	1	28
Present	17	7	24
Total	44	8	52

Chi-square test: df = 1, p = 0.01* (Statistically significant).

Table: 11 Association between cytokeratin positivity and disseminated tumour cells

Cytokeratin status	DTC Negative	DTC Positive	Total
Negative	44	2	46
Positive	0	6	6
Total	44	8	52

Chi-square test: df = 1, p = 0.001* (Statistically significant).

DISCUSSION

Ovarian carcinoma continues to have a high mortality rate due to late clinical presentation and early systemic dissemination [13]. Recent evidence challenges the traditional concept that

haematogenous spread occurs only in advanced disease, supporting the occurrence of early tumour cell dissemination [14,15]. Disseminated tumour cells (DTCs) in bone marrow have therefore been proposed as a surrogate marker of occult metastasis and potential prognostic indicator in ovarian carcinoma [16].

In the present study, DTCs were detected in 15.38% of patients, a prevalence lower than the 30–50% reported in Western studies [19,20]. Chebouti et al. reported DTC positivity in 41% of cases, suggesting geographic and methodological variability in detection rates [19]. Cytokeratin-positive epithelial tumour cells were identified in 11.54% of patients, confirming the epithelial origin of disseminated cells, consistent with findings by Braun et al. and Obermayr et al. [16,24].

No significant association was observed between DTC positivity and age, menopausal status, tumour stage, lymph node status, histological subtype, or TNM stage. Similar observations were reported by Judson et al., Poveda et al., and Obermayr et al., indicating that dissemination may occur independently of conventional clinicopathological parameters [21–24]. In contrast, studies by Sang et al. and Fan et al. demonstrated higher DTC detection in advanced-stage disease, highlighting biological heterogeneity among ovarian carcinomas [22,25].

A significant association was identified between vascular invasion and DTC positivity, supporting the hypothesis that vascular invasion facilitates early haematogenous spread [26]. The strong correlation between cytokeratin positivity and DTC detection further supports the role of DTCs as markers of minimal residual disease.

Overall, the findings suggest that bone marrow detection of disseminated tumour cells reflects early tumour dissemination in ovarian carcinoma and may serve as an independent prognostic indicator. Further longitudinal studies are required to establish its clinical utility in predicting recurrence and guiding therapeutic strategies.

CONCLUSION

Ovarian carcinoma is characterised by early and rapid tumour dissemination, which contributes substantially to high mortality rates and the development of resistance to standard treatment modalities. Early identification of systemic tumour spread at the time of diagnosis is therefore critical for accurate risk stratification and treatment planning. The present study demonstrates that disseminated tumour cells can be detected in the bone marrow of patients with ovarian carcinoma irrespective of age, menopausal status, tumour stage, lymph node involvement, histological subtype, or TNM stage, indicating that tumour dissemination may occur early and remain undetected by conventional clinicopathological assessment. The significant association between vascular invasion and disseminated tumour cell positivity supports the role of DTCs as markers of early haematogenous spread, while the

strong correlation with cytokeratin positivity confirms their epithelial origin and suggests the presence of minimal residual disease following surgical cytoreduction. From a clinical perspective, detection of DTCs may help identify patients at higher risk of disease persistence, early recurrence, and suboptimal response to standard therapy, thereby informing decisions regarding the intensity of adjuvant treatment and follow-up strategies. Prognostically, incorporation of bone marrow DTC assessment may complement existing staging systems by providing additional biological insight into tumour behaviour, with the potential to facilitate more individualised management and improve long-term outcomes in patients with ovarian carcinoma.

FIGURES

Figure 1: Photomicrograph of bone marrow smear showing clusters of malignant epithelial cells against a background of normal haematopoietic cells (Leishman stain, ×40).

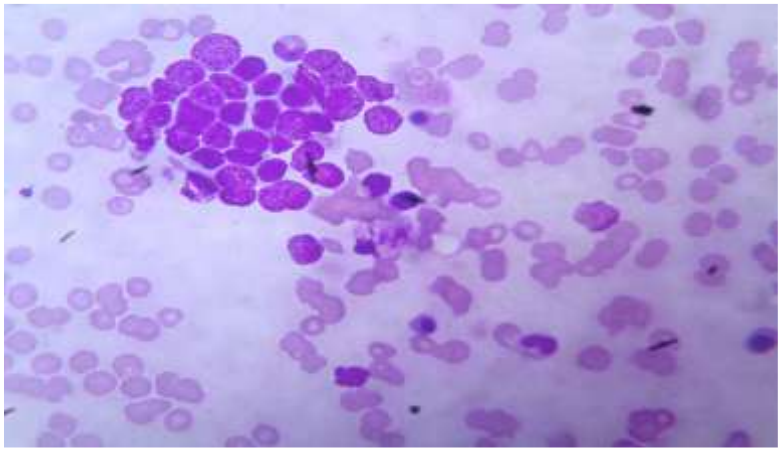


Figure 2: Bone marrow smear demonstrating clusters and scattered malignant epithelial cells amidst normal haematopoietic elements (Leishman stain, ×40).

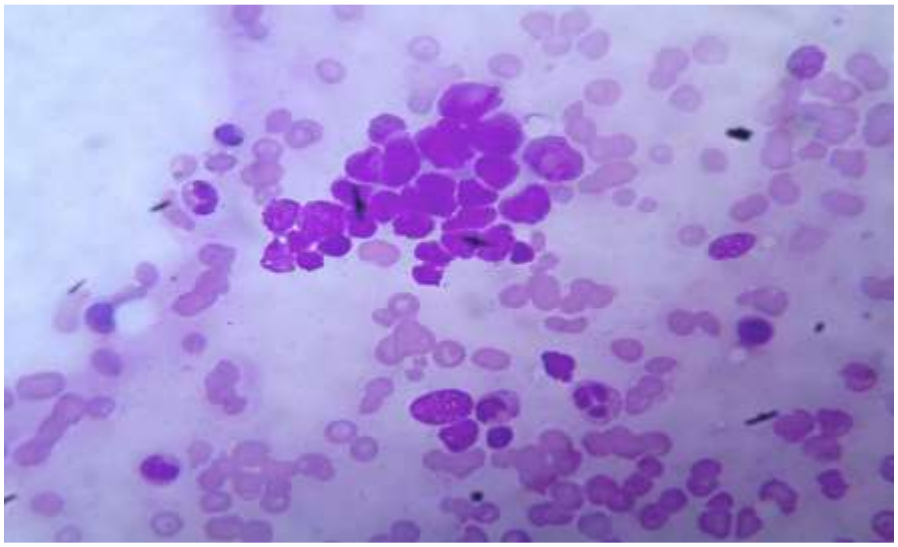


Figure 3: Photomicrograph showing cohesive clusters of malignant epithelial cells within bone marrow with preserved background haematopoietic cells (Leishman stain, ×40).

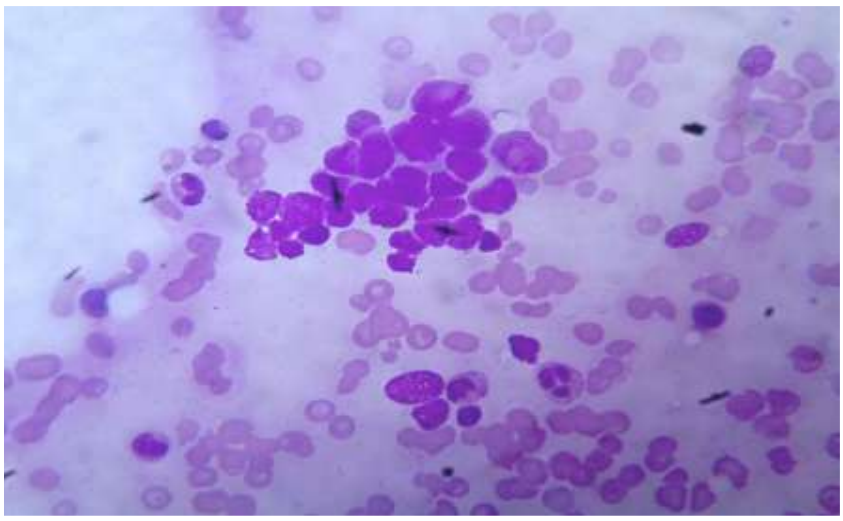


Figure 4: Bone marrow smear illustrating scattered and clustered malignant epithelial cells (Leishman stain, ×40).

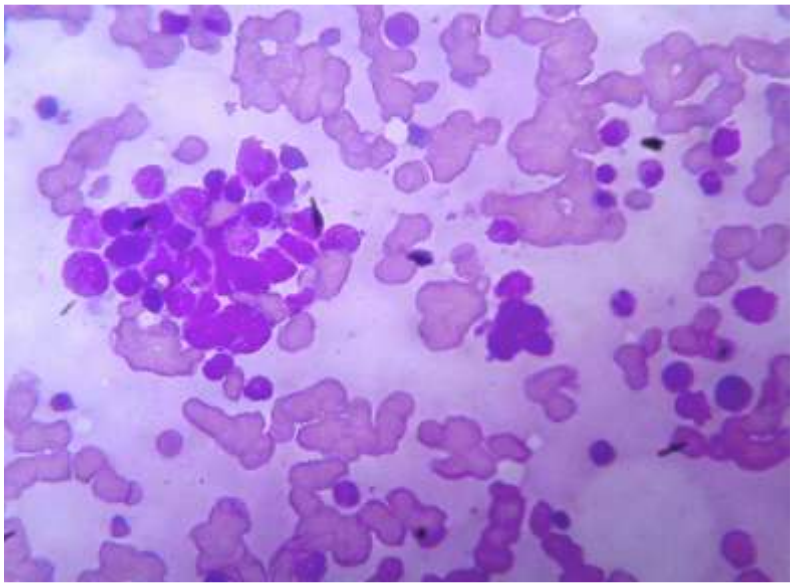


Figure 5: Photomicrograph showing disseminated tumour cells exhibiting positive immunoreactivity for pan-cytokeratin, confirming epithelial origin (Immunocytochemistry, ×40).

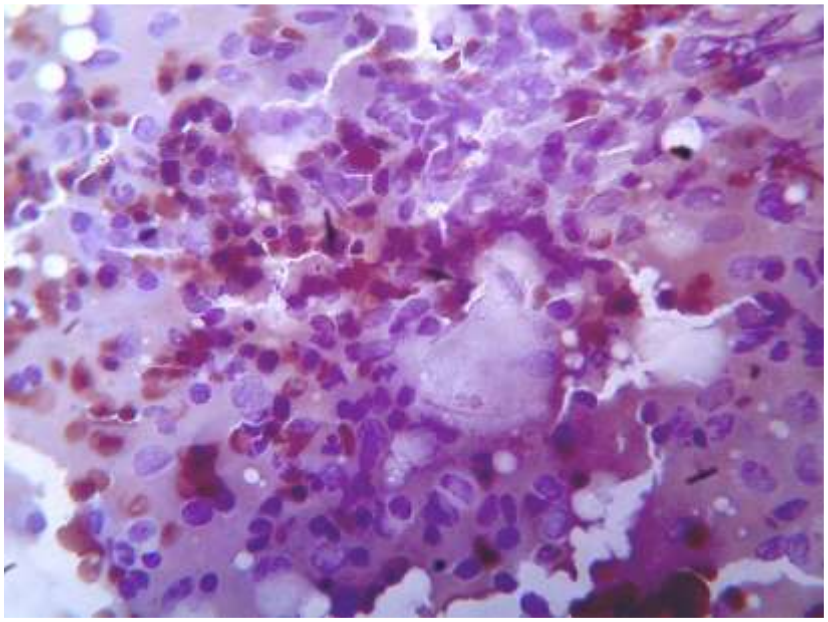
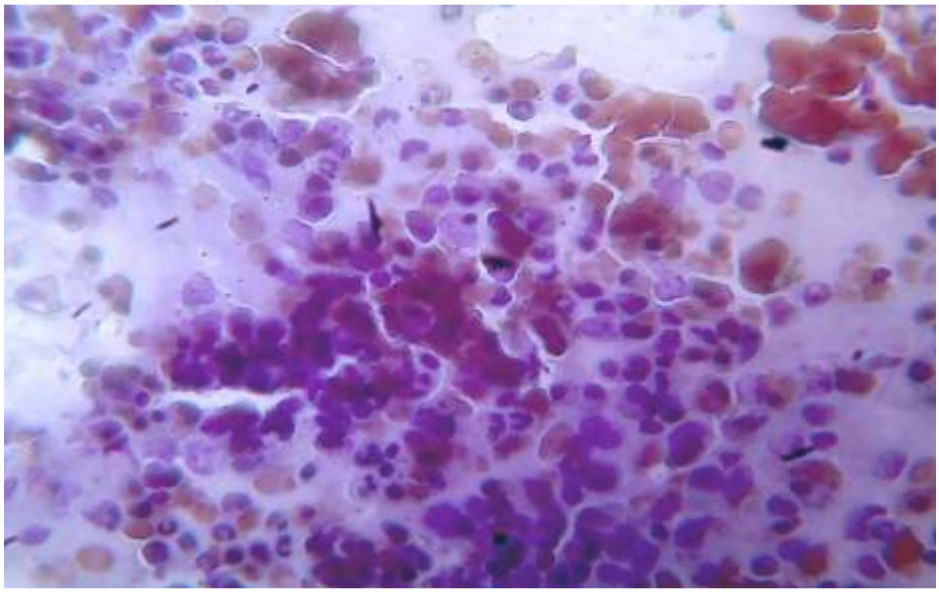


Figure 6: Photomicrograph demonstrating strong pan-cytokeratin positivity in disseminated tumour cells within bone marrow smear (Immunocytochemistry, ×40).



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