

Elevated preoperative neutrophil : lymphocyte ratio as a preoperative indicator of mature cystic teratoma with malignant transformation

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Abstract

Aim: To examine the usefulness of the neutrophil : lymphocyte (N/L) ratio as a cost-effective and simple diagnostic marker of mature cystic teratoma (MCT) with malignant transformation (MT).

Methods: A retrospective chart review was performed between 1998 and 2013 of 12 MCT patients with MT and between 2009 and 2013 of 130 patients with benign MCT. Data were collected on age, tumor size, white blood cell count with differential counts, tumor marker levels, and presenting features.

Results: Older age, greater tumor size, higher CA19-9 or CA125, higher neutrophil count, and higher N/L ratio were associated with MT on univariate analysis. White blood cell count; lymphocyte count; and the tumor marker squamous cell carcinoma antigen were not associated with MT. Older age (\geq median), larger tumor size (≥ 10 cm), and high N/L ratio (≥ 5.0) were predictors of MT (hazard ratio, 11.51, 5.87, and 11.11, respectively). Six of 12 patients were diagnosed with MT on preoperative magnetic resonance imaging and five of 12 had an N/L ratio ≥ 5.0 .

Conclusions: Neutrophil : lymphocyte ratio is a potential preoperative diagnostic marker of MT. The optimal cut-off should be determined in future large-scale studies.

Key words: biological marker, inflammation, neutrophil, ovarian neoplasm, teratoma.

Introduction

Mature cystic teratoma (MCT), a germ cell-type tumor, is the most common ovarian tumor, accounting for 10–20% of all ovarian tumors.¹ MCT with malignant transformation (MT) is especially rare, with an occurrence of 0.17–2%.^{2,3} Squamous cell carcinoma (SCC) is the major histological type of MT, accounting for 80–90% of cases. In some instances, a preoperative diagnosis is difficult, and a final diagnosis of MT is made unexpectedly on final pathological examination or intraoperatively. MT has a poorer prognosis than epithelial ovarian cancer, and there is currently no standardized chemotherapeutic regimen because of its rarity.^{4,5}

Inflammation is considered as an initiating factor of cancer, and the inflammatory cells that accumulate

within cancerous tissues play a crucial role in the neoplastic process by fostering proliferation, promoting survival, and facilitating migration.⁶ Moreover, inflammation, infection, and oncogene activation promote activation of several transcription factors, such as nuclear factor kappa-B (NF- κ B), signal transducer and activator of transcription 3 (STAT3), and hypoxia-inducible factor 1-alpha (HIF1 α), in tumor cells. The tumor cells then produce chemokines, cytokines, and prostaglandins, which recruit inflammatory cells, which then subsequently trigger cancer-related inflammation and further facilitate various tumor-promoting effects.⁷ The neutrophil : lymphocyte (N/L) ratio has been shown to reflect the immune response and has been identified as a prognostic marker in many cancers, including gastrointestinal tract malignancy, non-small cell lung cancer, cervical cancer,

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hepatocellular carcinoma, pancreatic cancer, ovarian cancer, and soft-tissue sarcoma, reflecting a consistently decreased survival in patients with a high N/L ratio.^{8–15} In addition, N/L ratio is reportedly correlated to incidental microcarcinoma in thyroid goiters, further indicating its potential as a diagnostic marker.¹⁶ Thus, N/L ratio could represent a simple and cost-effective tool to diagnose ovarian malignancies. Given that MT is often difficult to diagnose preoperatively, the aim of the current study was to assess the value of the preoperative N/L ratio as a diagnostic marker to distinguish MCT with MT from benign MCT.

Methods

Subjects

We retrospectively reviewed the medical charts of 12 MT patients who underwent surgery between July 1998 and September 2013, and 130 benign MCT patients who underwent surgery between April 2009 and January 2013 at Keio University Hospital (Tokyo, Japan) or Ashikaga Red Cross Hospital (Tochigi, Japan). Demographic, clinical, pathological, and laboratory data, including patient age, tumor size, white blood cell (WBC) count with differential counts, tumor marker levels, and presenting features, were recorded. We excluded those who were pregnant at the time of surgery. We also excluded cases of emergency surgery due to torsion or rupture of ovarian tumor. WBC count with differential counts was measured using the XE-5000 Hematology Analyzer system (Sysmex, Kobe, Japan). Serum CA19-9 and CA125 were measured using the Modular Analytics E170 Immunoassay Analyzer (Hoffmann-La Roche, Basel, Switzerland). Serum SCC antigen (SCC-Ag) was measured using the Architect Analyzer i2000 Immunoassay Analyzer (Abbott Laboratories, Chicago, IL, USA). The normal range for total WBC count at Keio University Hospital is $4\text{--}10 \times 10^9$ cells/L, and the normal range of neutrophils and lymphocytes is 50–70% and 20–40%, respectively. The N/L ratio was calculated from the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count. An N/L ratio ≥ 5 was considered elevated in accordance with the literature.^{8,11,17,18}

Statistical Analysis

Mann–Whitney test was used for univariate analysis, and a logistic regression model for multivariate analysis. Hazard ratios (HR) were estimated from the logistic regression analysis and reported with 95%CI. $P < 0.05$ was considered statistically significant. Statistical

analysis was performed using IBM SPSS Statistics for Windows, Version 23. (IBM-Corp., Armonk, NY, USA).

Results

Patient Characteristics

Among the 12 MT patients, six, three, two, and one were diagnosed with stage I, II, III, and IV disease, respectively. The MT histological type was SCC in nine patients and adenocarcinoma in three patients (Table 1).

N/L Ratio and Clinicopathological Factors

We first evaluated the relevance of several reported factors and WBC, neutrophil, and lymphocyte counts, as well as the N/L ratio, with the incidence of MT and MCT (Table 2). Older age ($P = 0.003$), greater tumor size ($P = 0.001$), higher CA125 ($P = 0.035$) or CA19-9 ($P = 0.022$) were associated with MT. The median age of the MT group (49.5 years) was concordant with that in previous reports noting that the incidence of MT peaks in the range 45–60 years.³ At the same time, higher neutrophil count ($P = 0.011$) and N/L ratio ($P = 0.002$) were associated with MT. Although the N/L ratio had an association with MT in particular, WBC and lymphocyte count were not associated with MT. Moreover, the tumor marker SCC-Ag was not associated with MT ($P = 0.682$). Hence, we propose that a higher neutrophil count is a predictor of MT ($P = 0.011$), while N/L ratio more accurately indicates an association with MT ($P = 0.002$). These data indicate that the N/L ratio is more sensitive to MT than the tumor marker SCC-Ag, which is routinely used in the clinical setting.

Furthermore, on multivariate analysis of the three factors associated with MT on univariate analysis (age [$<$ median vs \geq median], tumor size [<10 cm vs ≥ 10 cm], and N/L ratio [< 5.0 vs ≥ 5.0]), all were found to be associated with MT. In particular, older age, larger tumor size, and high N/L ratio were significant predictive

Table 1 Baseline MT patient characteristics

Characteristics	<i>n</i> = 12
FIGO stage	
I	6
II	3
III	2
IV	1
Histology	
SCC	9
Adenocarcinoma	3

FIGO, The International Federation of Gynecology and Obstetrics; MT, malignant transformation; SCC, squamous cell carcinoma.

Table 2 Univariate indicators of MT

	MT (<i>n</i> = 12)		MCT (<i>n</i> = 130)		<i>P</i> - value
	Median	(range)	Median	(range)	
Age (years)	49.5	(27–70)	34	(14–78)	0.003**
Tumor size (cm)	11.75	(6.5–23)	6.15	(1–28)	0.001**
WBC (cells/mm ³)	5800	(4600–14 300)	5400	(3000–11 900)	0.062
Neutrophils (cells/mm ³)	4493	(1900–11 655)	3336	(1067–8056)	0.011*
Lymphocytes (cells/mm ³)	1378	(720–1900)	1632	(705–4165)	0.155
N/L ratio	3.575	(1.0–8.4)	2	(0.4–9.9)	0.002**
CA125 (U/mL)	63	(7–145)	19	(6–1228)	0.035*
CA19-9 (U/mL)	156	(12–1204)	27	(1–424)	0.022*
SCC-Ag (ng/mL)	2.75	(0.2–24.9)	1.1	(0.5–7.2)	0.682

P* < 0.05, *P* < 0.01. CA125, cancer antigen 125; CA19-9, cancer antigen 19-9; MCT, mature cystic teratoma; MT, malignant transformation; N/L ratio, neutrophil : lymphocyte ratio; SCC-Ag, squamous cell carcinoma antigen; WBC, white blood cells.

indicators of MT with HR of 11.51, 5.87, and 11.11, respectively (Table 3).

Given that preoperative diagnosis of MT is often difficult, we compared preoperative diagnosis on magnetic resonance imaging (MRI) with that on N/L ratio for each case of MT. As shown in Table 4, six of 12 patients were diagnosed with MT on preoperative MRI, and five of 12 patients had an N/L ratio ≥ 5.0 . All patients with N/L ratio ≥ 5.0 were diagnosed with MT on MRI, indicating that MRI diagnosis of MT is well correlated with high N/L ratio. Histology was not correlated with either N/L ratio or MRI diagnosis.

Discussion

In this study, we investigated the potential of N/L ratio for use as a simple and economical diagnostic tool. The fact that cancer patients with a high N/L ratio have poorer clinical outcome in various neoplasms indicates a strong correlation between inflammation and cancer. Inflammation is an important factor in the initiation of cancer, as illustrated by hepatitis C virus infection in hepatic cancer, *Helicobacter pylori* infection in gastric cancer, and inflammatory bowel disease in colon cancer. We showed that a high N/L ratio is associated with MT, indicating that inflammation plays an important role in MT. Indeed, high-risk human papilloma virus infection

is reported to be associated with SCC of the ovary.^{19,20} Given that the mechanisms of MT remain unclear, basic approaches based on inflammation offer a good starting point for MT research.

The N/L ratio is sufficient to estimate the risk of MT, but the sensitivity and specificity are the same as those for MRI, and it was difficult to identify early MT lesions in the present study. Nonetheless, N/L ratio is as accurate as age and tumor size to predict MT.²¹ Given that monitoring of N/L ratio is a simple and cost-effective diagnostic method to predict the incidence of MT, it presents a complementary, efficient method to support a preoperative diagnosis of MT. In this study, we used an N/L ratio cut-off of 5.0, which is considered high,^{8,11,17,18} due to the rarity of reported MT cases with which to determine a cut-off based on receiver operating characteristic curve analysis. Also, N/L ratio is reportedly an indicator of incidental microcarcinoma,¹⁶ therefore it may be useful to detect early cancer difficult to detect on MRI. Thus, more accurate cut-offs for N/L ratio will need to be determined in future large-scale studies.

Of the gynecologic malignancies, endometrial cyst formation of the ovary is a primary source of ovarian cancer. In addition, inflammation at the ovarian surface epithelium and fallopian tube is proposed to be closely involved in epithelial ovarian cancer initiation.²² Thus, it would be intriguing to determine whether N/L ratio

Table 3 Multivariate indicators of MT

Variable	HR	95%CI	<i>P</i> - value
Age (<median vs \geq median)	11.51	1.11–119.06	0.040*
Tumor size (<10 cm vs \geq 10 cm)	5.87	1.13–30.47	0.035*
N/L ratio (<5.0 vs \geq 5.0)	11.11	1.40–87.88	0.023*

**P* < 0.05. MT, malignant transformation; N/L ratio, neutrophil : lymphocyte ratio.

Table 4 Preoperative N/L ratio vs MRI diagnosis

Histology	N/L ratio	MRI diagnosis
SCC	1.00	Benign
SCC	1.88	Benign
SCC	2.48	Benign
Adenocarcinoma	2.54	MT
Adenocarcinoma	2.89	Benign
SCC	3.01	Benign
SCC	4.14	Benign
SCC	5.30	MT
SCC	6.25	MT
SCC	6.27	MT
Adenocarcinoma	6.83	MT
SCC	8.40	MT

MRI, magnetic resonance imaging; MT, malignant transformation; N/L ratio, neutrophil : lymphocyte ratio; SCC, squamous cell carcinoma.

is a suitable predictor of ovarian cancer in patients with endometrial cyst.

The usefulness of tumor markers has been investigated in several studies, with varying results. It was surprising that serum SCC-Ag was not associated with MT in the present study. The reason seems to be that SCC-Ag is high in some benign MCT, concordant with a previous report.²¹ Mori *et al.* reported on the usefulness of combining SCC-Ag with age as a predictor of MT.²³

In conclusion, N/L ratio is a simple diagnostic marker of MT. The complementary use of N/L ratio may also be a simple and effective method to distinguish MCT with MT from benign MCT.

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Disclosure

The authors declare no conflict of interest.

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