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Analysis of Histologic Parameters Associated with Nuclear Size in Diffuse Malignant Peritoneal Mesothelioma Uniformly Treated by Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

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Abstract

Aims: Nuclear size has been identified as a significant prognostic indicator for survival after cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma (DMPM). The additional histopathologic features associated within the clinical material have not been determined. This current study assessed the correlations between nuclear size and 12 other histopathologic parameters.

Methods: A review of the histopathological features of DMPM in 62 patients who underwent uniform management of cytoreductive surgery and perioperative intraperitoneal chemotherapy was performed. Nuclear size was categorized into two groups: ≤ 30 μ.m (n = 35) versus > 30 μ.m (n = 27). The correlations between nuclear size and 12 histopathologic parameters of DMPM were determined by univariate analysis.

Results: Patients with nuclear size > 30 μ.m had a less favorable prognosis, as compared to patients with nuclear size ≤ 30 μ.m ($p < .001$). Nuclear size was statistically correlated with histologic type ($p = .012$), nuclear/cytoplasmic ratio ($p < .001$), mitotic count ($p = .001$), atypical mitosis ($p < .001$), tumor necrosis ($p < .001$), chromatin pattern ($p < .001$) and nucleolar size ($p < .001$).

Conclusions: Histopathologic features present along with nuclear size are histologic type, nuclear/cytoplasmic ratio, mitotic count, atypical mitosis, tumor necrosis, chromatin pattern and nucleolar size in patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy. The identification of these histopathologic features may function as an adjunct to nuclear size in the estimation of prognosis.

Introduction

Several studies have documented that DMPM consists of heterogeneous histopathologic features [1-3]. In 1995 Goldblum and Hart first proposed a mesothelioma nuclear grading system which categorized the histomorphology of DMPM into four grades: Grade 0 represented small nuclei, uniform chromatin pattern and inconspicuous or absent nucleoli; Grade 1 represented small nuclei, uniform chromatin pattern and small pinpoint-sized nucleoli; Grade 2 represented large nuclei, some chromatin irregularity and more prominent nucleoli; and Grade 3 represented large nuclei, irregular chromatin pattern with clearing and prominent macronucleoli [3]. However, the number of patients studied did not allow a statistical assessment of the grading system to test its clinical value. Recently, Nonaka and co-workers demonstrated an improved survival in patients with low-grade nuclei after cytoreductive surgery and perioperative intraperitoneal chemotherapy [4]. Cerruto and colleagues used a group of 62 DMPM patients treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy to search for histologic parameters that correlated with prognosis [5]. In this study they identified nuclear/nucleolar size as the most reliable single parameter by which to predict outcome. The current study attempts to identify other histologic features that can act as an adjunct to nuclear size in the histopathologic estimation of prognosis in DMPM patients to be treated by cytoreductive surgery and perioperative intraperitoneal chemotherapy.

Patients and Methods

Patient Selection

Sixty-two consecutive patients with a diagnosis of DMPM were treated in a uniform fashion utilizing cytoreductive surgery combined with perioperative intraperitoneal chemotherapy by the same surgical team at the Washington Cancer Institute, Washington, DC. These 62 patients formed the basis of this report. The clinical data were obtained prospectively and entered regularly into an electronic database by a research assistant. All patients were followed prospectively until the last time of contact or death.

Preoperative Management

All patients underwent extensive preoperative evaluations, including physical examination, abdominal, pelvic and chest CT to assess the extent of the disease. Measurements of relevant tumor markers (e.g., CA 15-3, CA 19-9, CA 72-4, CA 125 and Carcino-embryonic antigen) were also obtained.

Cytoreductive Surgery

The details of the surgical techniques have been described

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elsewhere. In short, a midline incision was made from the xiphoid to the pubic symphysis. The edges of the incision were retracted bilaterally. Peritonectomy procedures were performed with electroevaporative surgery using a ball-tipped diathermy [6]. Cytoreductive surgery consisted of a series of peritonectomy procedures including: anterior parietal peritonectomy, greater omentectomy with splenectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, lesser omentectomy with cholecystectomy, and pelvic peritonectomy with rectosigmoid or total colonic resection [7]. The visceral resections included rectosigmoidectomy, right colectomy, total abdominal colectomy, hysterectomy and small bowel resection. These resections were used at anatomic sites where there was visible evidence of disease. All mesothelioma invasion or entrapment of the resected specimens was documented by histopathologic examination.

Perioperative Intraperitoneal Chemotherapy

After maximal cytoreduction of peritoneal mesothelioma, the skin edges were elevated on a self-retaining retractor to make a reservoir of the abdomen and pelvis to retain the chemotherapy solution. Intraperitoneal hyperthermic chemotherapy with cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2) was administrated in the operating room at approximately 41.5°C in 3 L of 1.5% dextrose peritoneal dialysis solution for 90 minutes [8]. The intraperitoneal chemotherapy solution was manually distributed to facilitate uniform distribution and penetration of the chemotherapy into residual tumor.

In the early postoperative period (postoperative day 1 to day 5), paclitaxel at 20 mg/m^2/day was administered into the peritoneal cavity in 1 L of 1.5% dextrose peritoneal dialysis solution or 6% hetastarch solution [9]. Nasogastric suctioning, thoracostomy drainage of the pleural spaces, total parental nutrition, deep venous thrombosis prophylaxis and postoperative pain control were used as indicated in the DMPM clinical pathway.

Histologic Materials

A comprehensive review of the histopathological features of DMPM was performed by two pathologists, who individually evaluated each case. These two pathologists were aware that all 62 patients in this study had clinical evidence of peritoneal mesothelioma but were masked to all other clinical information. The mean number of specimens taken from separate anatomic sites was [11] + 4 per patient. The mean number of slides studied was 20 + 8 per patient. The assessment and measurement of the histopathological features were finally determined by the predominant findings throughout the multiple specimens examined in each case. Any differences in the interpretation of these slides were resolved by final consensus between the two pathologists.

The immunohistochemical studies were performed using immunostaining on formalin-fixed, paraffin-embedded sections using the avidin-biotin-peroxidase complex method. Sections were cut 3-4 μ.m thick, deparaffinized in xylene, and rehydrated in descending grades (100-70%) of ethanol. Endogenous peroxidase activity was blocked by a 10-minute treatment with 3% hydrogen peroxide in absolute methanol. The primary antibodies used were keratin 5/6 by Boehringer-Mannheim (Indianapolis, IN), 1:25 dilution Calretinin by Zymed Laboratories, Inc. (South San Francisco, CA) pre-diluted by the manufacturer; Ber-EP4 by DakoCytomation California Inc. (Carpinteria, CA) 1:30 dilution; and B72.3 by Signet Laboratories Inc. (Dedham, MA) 1:30 dilution. All cases selected were positive for Calretinin and CK 5/6 and negative for at least two epithelial markers including B72.3 and Ber-EP4 [10].

Histopathologic Parameters

The nuclear size was determined using red blood cells within the microscopic field of view as a reference diameter of approximately 7 μ.m. Magnification of 40x was used during this measurement. The measurement was of the predominant nuclei size found throughout the multiple specimens examined. For this study, nucleus size was categorized into two groups: ≤ 30 μ.m versus > 30 μ.m. The ≤ 30 μ.m diameter nuclei were ≤ four times the RBC diameter; the > 30 μ.m diameter nuclei were > four times the RBC diameter. These measurements of the DMPM nuclei were supplemented by a micrometer. The mesothelioma cell differentiation was categorized by using a histological grading system recommended by the American Joint Cancer Commission [11]. It was based on a qualitative assessment of the differentiation of a tumor expressed as the extent to which a tumor resembled the normal tissue of the primary cancer site. It ranged from well-differentiated to moderately-differentiated to poorly-differentiated and was evaluated strictly by architectural appearance of a given neoplasm. DMPM was well-differentiated, if clear recognition of tubular, papillary, cystic, or a combination of these patterns were seen. DMPM was scored as poorly-differentiated, if tubular, papillary and cystic structures were greatly substituted by solid sheets of tumor. In the moderate-differentiated cases there was a significant loss of the well-differentiated pattern; however poorly-differentiated segments were not so predominant.

DMPM were classified into epithelial, biphasic or sarcomatoid histologic types, according to the World Health Organization classification [12]. The nuclear/cytoplasmic ratio was evaluated at 40x magnification and categorized into normal versus increased nuclear/cytoplasmic ratio. Mitotic count was evaluated in 10 high-power microscopic fields (HPF) at 40x and categorized into ≤ 4 versus > 4. Histopathologic features of atypical mitosis, tumor necrosis, pleomorphism, perineural invasion and lymph nodal involvement were designated as absence versus presence. Depth of invasion of visceral specimens was also studied as either superficial or deep. Superficial invasion was classified when the malignant cells limited to the subserosal layer. Deep invasion was classified when tumor cells were evident in the deeper layers of the bowel (i.e. muscularis propria, submucosa and mucosa).

The chromatin pattern of the nucleus was evaluated by the distribution of chromatin material. In normal or reactive mesothelial cells the chromatin pattern was usually uniform and granular. In some cases it was noted that nuclei would have a clear chromatin pattern. The chromatin pattern was classified into two groups: uniform and granular versus clear.

Nucleolar size was determined using a reticle installed in a light microscope and categorized into ≤ 3 μ.m versus > 3 μ.m.

Statistical Analysis

Institutional review board approval was obtained to analyze these data. Survival analysis was performed by using Kaplan-Meier method and compared using the log rank test. The correlations of nuclear size and 12 histopathologic parameters were determined by univariate analysis using Chi [2]. (or Fisher's exact) test. All statistical analyses were performed using SPSS for Windows (Version 11.5; SPSS GmbH, Munich, Germany). A significant difference was assumed for a p-value less 0.05.

Results

Clinical Data

There were 34 male patients (55%). The mean age at the time of

diagnosis of DMPM was 47 +13 years. The mean age at the time of surgery was 49 +13 years. All patients were followed until October 1, 2005 or until death. The median follow-up was 37 months (range 8 to 143 months). Thirty-six patients (58%) were alive at the last time of contact.

Survival Results

The overall median survival was 79 months (range 1 to 143 months), with 1-, 3- and 5-year survival rates of 84%, 58% and 50%, respectively. The 1-, 3- and 5year survival of patients with nucleus size ≤ 30 μ.m were 100%, 90% and 77%, respectively. The 1-, 3- and 5-year survival of patients with nucleus size > 30 μ.m were 62%, 37% and 18%, respectively. The prognostic significance of nuclear size for overall survival was p < .001 (Figure 1)

Histopathologic Results

The mean nuclear size was 3 +10 μ.m. Thirty-five patients had nuclear size of ≤ 30 μ.m and 27 patients had nuclear size > 30 μ.m. Table 1 demonstrates the correlations between nuclear size and 12 histopathologic parameters, including cell differentiation, histologic type, nuclear/cytoplasmic ratio, mitotic count, atypical mitosis, tumor necrosis, pleomorphism, perineural invasion, lymph nodal involvement, depth of invasion chromatin pattern and nucleolar size by univariate analysis.

Histologic type (p = .012) (Figure 2), nuclear/cytoplasmic ratio (p < .001) (Figure 3), mitotic count (p = .001) (Figure 4), atypical mitosis (p < .001) (Figure 5) and tumor necrosis (p < .001) (Figure 6) were strongly correlated with nuclear size.

Chromatin pattern and nucleolar size were 100% correlated with nuclear size. All 35 patients with nuclear size of ≤ 30 μ.m had uniform/granular chromatin pattern and nucleolar size of ≤ 3 μ.m (Figure 7). In contrast all 27 patients with nuclear size > 30 μ.m had clear chromatin pattern and nucleolar size of > 3 μ.m (Figure 8).

Discussion

Evolution in the management of DMPM has occurred over the last two decades [11]. Cytoreductive surgery combined with perioperative

Variable	Nuclear Size		Chi² P-value
	≤ 30 μm n (%)	> 30 μm n (%)	
Total	35 (100)	27 (100)	-
Cell differentiation	-	-	1.000
Well/moderately differentiated	24 (69)	19 (70)	-
Poorly differentiated	11 (31)	8 (30)	-
Histologic type	-	-	.012
Epithelial	35 (100)	22 (82)	-
Biphasic	0 (0)	5 (18)	-
Nuclear/cytoplasmic ratio	-	-	< .001
Normal	33 (94)	9 (33)	-
Increased	2 (6)	18 (67)	-
Mitotic count	-	-	.001
≤ 4	34 (97)	17 (63)	-
> 4	1 (3)	10 (37)	-
Atypical mitosis	-	-	< .001
Absent	35 (100)	16 (59)	-
Present	0 (0)	11 (41)	-
Tumor necrosis	-	-	< .001
Absent	31 (89)	12 (44)	-
Present	4 (11)	15 (56)	-
Pleomorphism	-	-	.359
Absent	29 (83)	19 (70)	-
Present	6 (17)	8 (30)	-
Perineural invasion	-	-	.279
Absent	32 (91)	22 (82)	-
Present	3 (9)	5 (19)	-
Lymph nodal involvement	-	-	.223
Absent	33 (94)	22 (82)	-
Present	2 (6)	5 (18)	-
Depth of invasion	-	-	.124
Infiltration limited to subserosal layer	24 (69)	13 (48)	-
Infiltration beyond subserosal layer	11 (31)	14 (52)	-
Chromatin Pattern	-	-	< .001
Uniform/granular	35 (100)	0 (0)	-
Clear	0 (0)	27 (100)	-
Nucleolar size	-	-	< .001
≤ 3 μm	35 (100)	0 (0)	-
> 3 μm	0 (0)	27 (100)	-

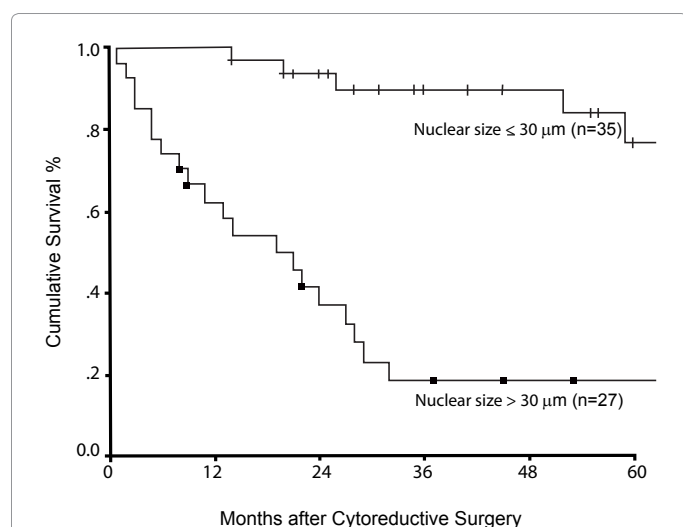**Table 1:** Correlations between nuclear size and 12 other histopathologic parameters.

Figure 1: Survival by nuclear size after cytoreductive surgery and perioperative intraperitoneal chemotherapy for patients with diffuse malignant peritoneal mesothelioma (n = 62). Prognostic significance of nuclear size was p < .001.
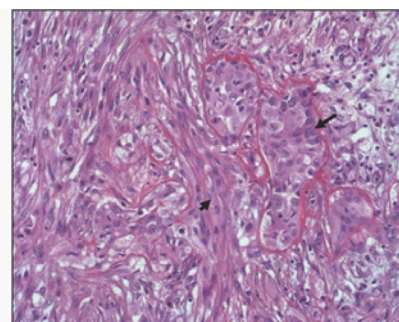

Figure 2: Biphasic type of diffuse malignant peritoneal mesothelioma at 20x shows features of both sarcomatoid (short arrow) and epithelial (long arrow) types, characterized by spindle-looking mesothelial cells within nests of epithelial mesothelial cells.
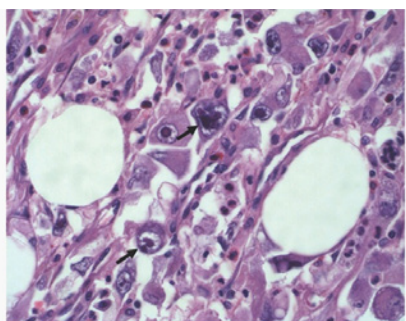
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Figure 3: Diffuse malignant peritoneal mesothelioma at 40x shows increased nuclear/cytoplasmic ratio (long arrow).

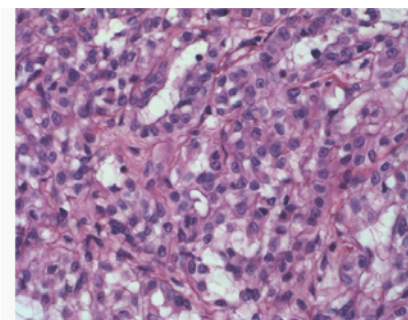**Figure 7:** Diffuse malignant peritoneal mesothelioma at 40x shows nuclear size of ≤ 30 μm, uniform/granular chromatin pattern and nucleolar size of ≤ 3μm.
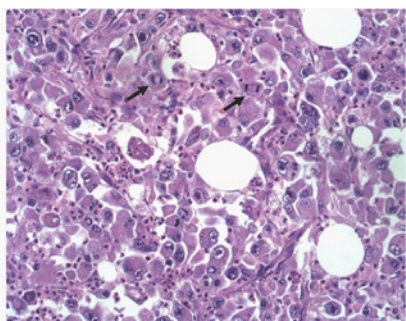

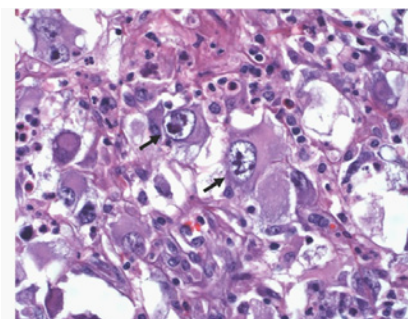**Figure 4:** Diffuse malignant peritoneal mesothelioma at 20x shows presence of mitosis (long arrow).

Figure 8: Diffuse malignant peritoneal mesothelioma at 40x shows nuclear size > 30 μm, clear chromatin pattern and nucleolar size of > 3 μm (long arrow).
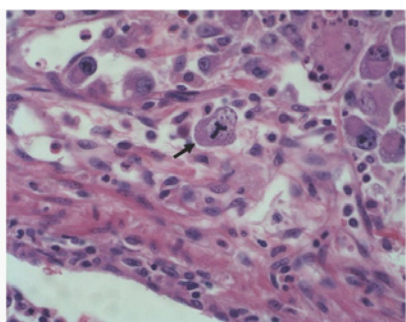

Figure 5: Diffuse malignant peritoneal mesothelioma at 40x shows presence atypical mitosis (long arrow).
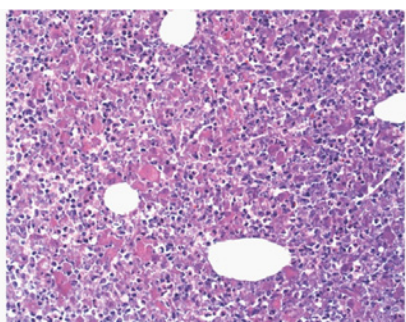

Figure 6: Diffuse malignant peritoneal mesothelioma at 20x shows presence of tumor necrosis.

intraperitoneal chemotherapy is a comprehensive treatment alternative that has become available in recent years. Several international centers have reported an improved survival in selected patients with DMPM who were treated with this combined modality, achieving a median survival of 50 to 90 months [12-16]. As more patients are treated in this uniform manner, a meaningful clinic pathologic study of this rare disease is made possible.

There is a great variation in histopathologic features exists in DMPM. In 1995 a nuclear grading system was first described by Goldblum and Hart based on histomorphologic interpretations of mesothelioma nuclear size, chromatin pattern and nucleolar size [3]. The authors found that tumors with a low-grade nuclei tended to be less aggressive. This interesting observation was further validated by Nonaka and colleagues, who demonstrated that low-grade nuclei were associated with an improved survival in DMPM patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy [4]. However, the nuclear grading system used in this report did not quantitate the nuclear size. Consistent histopathologic grading by different pathologists was difficult. Previously, our group characterized the histomorphologic features of DMPM, but no attempt was made to identify the correlations among these parameters [5].

As our study of the histomorphology of the peritoneal mesothelioma cell continued, it became evident that measurement of the cell nucleus using a micrometer was not consistent. The shrinkage of tissues in different case material varied considerably. Also, there were differences between the fixation of very large tumor specimens received from the operating room (i.e., the greater omentum) and thin specimens (i.e., strips of peritoneum). Also, we found that micrometers on different light microscopes were difficult to calibrate in exactly the

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same manner. Finally, adding to our difficulties was the fact that only a few light microscopes used in the reading of these slides were equipped a micrometer. After considerable rereading of slides and discussion, the red cell nucleus was retained as the standard of measurement for this nuclear grading scale.

There was a second change in our standard procedures for the use of nuclear size in assessing prognosis as compared to the original manuscript by Cerruto et al. [5]. Our original report utilized four sizes of nucleus for prognostication. In this report the original Class I and Class II nuclei are combined into a Group I. The classification III and IV were placed together into a Group II. This simplification of the reading of nuclear size was designed to provide an easier assessment (estimation) for utilization of this information by the general pathologist.

Although nuclear size has also been proposed as a staging system in other malignancies such as renal cell carcinoma and breast cancer, the assessment of nuclear size in DMPM is unfamiliar to most pathologists and the correlations of nuclear size with other histopathologic parameters has not been previously studied. With a hypothesis that nuclear size might reflect the biological behavior of DMPM, we performed a statistical assessment of the correlations between nuclear size and 12 histopathologic parameters.

These data showed 100% correlation of nuclear size with chromatin pattern and nucleolar size. All 35 patients with nuclear size of ≤ 30 μ.m had uniform/granular chromatin pattern and nucleolar size of ≤ 3 μ.m. In contrast, all 27 patients with nuclear size > 30 μ.m had clear chromatin pattern with or without intracellular inclusions and nucleolar size of > 3 μ.m. These findings show that there is a remarkable consistency between nuclear size, chromatin pattern and nucleolar size in DMPM. These data statistically supports the original nuclear grading system proposed by Goldblum and Hart [3]. These data confirm that a nuclear grading system that includes nuclear size, chromatin pattern, and nucleolar size is of value in a histologic assessment of prognosis in this disease DMPM.

It showed that nuclear size > 30 μ.m was strongly associated with biphasic histologic type, increased nuclear/cytoplasmic ratio, > 4 mitotic count, presence of atypical mitosis, presence of tumor necrosis, clear chromatin pattern and nucleolar size > 3 μ.m.

Three studies have demonstrated that increased mitotic count was associated with a less favorable prognosis in DMPM patients [4,17,18]. Also, the presence of increased nuclear/cytoplasmic ratio, atypical mitosis and tumor necrosis is correlated with the nuclear size and could be used to predict survival. However, the correlations with nuclear size in these parameters were not as perfect as chromatin pattern and nuclear size. As suggested by Cerruto and colleagues, these parameters could be used as minor prognostic criteria.

Although much progress has been made, greater insight regarding the clinical implications of these findings is required. Since such distinct survival differences are recognized, modification of treatment plans for patients with a high nuclear grade is warranted. For example, neoadjuvant systemic chemotherapy with pemetrexed and cisplatin may be indicated in this less favorable group prior to initiating the local-regional treatment option with cytoreductive surgery and perioperative chemotherapy.

In summary, DMPM Grade I nucleus is seen as a favorable prognosis with a median survival that was not reached at 5 years. The Group I nuclei are ≤ 30 μ.m in diameter (≤ 4x the RBC diameter seen in the field of view). An adjunctive finding to be expected in a study of this clinical method is a nucleolus ≤ 3 μ.m ($<$ half the RBC diameter) and chromatin of a granular pattern. The Group II nuclei are seen in poor prognosis patients with a median survival of approximately 20 months. The nuclear size of > 30 μ.m in diameter (> 4x the RBC diameter seen in the field of view) was associated with the nucleolus of > 3 μ.m ($<$ half the RBC diameter) and has a clear nuclear chromatin.

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