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Gliomatosis peritonei: a clinicopathologic and immunohistochemical study of 21 cases

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Gliomatosis peritonei, a rare condition often associated with immature ovarian teratoma, is characterized by the presence of mature glial tissue in the peritoneum. We retrospectively evaluated 21 patients with gliomatosis peritonei and studied their clinicopathologic features and immunophenotype. The patients' ages ranged from 5 to 42 years (median, 19 years). Their primary ovarian tumors consisted of immature teratoma ($n=14$), mixed germ cell tumors ($n=6$), and mature teratoma with a carcinoid tumor ($n=1$). Gliomatosis peritonei was diagnosed at the same time as primary ovarian neoplasm in 16 patients and secondary surgery in 5 patients. Also, 11 of 21 patients had metastatic immature teratoma ($n=4$), metastatic mature teratoma ($n=2$), or both ($n=5$). One patient developed glioma arising from gliomatosis peritonei. Seventeen patients had follow-up information and were alive with no evidence of disease ($n=13$), alive with disease ($n=3$), or alive with an unknown disease status ($n=1$). The follow-up durations ranged from 1 to 229 months (mean, 49 months; median, 23 months). Immunohistochemistry results demonstrated that SOX2 was expressed in all cases of gliomatosis peritonei and glioma with tissue available (nine of nine cases), whereas OCT4 and NANOG were negative in all cases with available tissue (eight of eight cases). In conclusion, both gliomatosis peritonei and glioma arising from it show a SOX2+/OCT4 − /NANOG − immunophenotype. These findings demonstrated that gliomatosis peritonei is associated with favorable prognosis, although it is important to rule out potentially associated immature teratoma and malignant transformation. SOX2 may have an important role in the development of gliomatosis peritonei.
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Gliomatosis peritonei, which is characterized by mature glial tissue in the peritoneum, is a rare condition usually associated with immature ovarian teratoma[1–5] and in rare cases with ventriculoperitoneal shunting.[6–8] Pathologically, gliomatosis peritonei is considered to be grade 0 teratoma according to the World Health Organization grading system used for immature teratoma.[9] The presence of gliomatosis peritonei, regardless of its extent, is usually not associated with adverse outcomes,[10] however, gliomatosis peritonei has been reported to transform into malignant glial neoplasms.[11,12] The origin of gliomatosis peritonei is also poorly understood.

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In the present study, we examined the clinicopathologic features of gliomatosis peritonei in 21 patients and the expression of a panel of stem cell markers consisting of POU5F1 (POU domain, class 5, transcription factor 1), also known as octamer-binding transcription factor 4 (OCT4), homeobox protein NANOG, and sex determining region Y-box 2 (SOX2).

Materials and methods

Tissue Specimens

A search of the pathology files at the University of Texas, MD Anderson Cancer Center from 1988 to 2014 performed after Institutional Review Board approval of the study identified 21 cases of gliomatosis peritonei. Relevant clinical data on the patients were obtained via retrospective review of the patients' medical files. These data included

demographic information, diagnosis, and tumor grade. Their follow-up information was updated through June 2015 via review of their medical records and tumor registration. Hematoxylin and eosin (H&E)-stained slides containing tissue sections of gliomatosis peritonei were reviewed. Paraffin-embedded tissue blocks ($n=8$) and an unstained slide containing gliomatosis peritonei and/or glioma were used for immunohistochemical staining for SOX2, OCT4, and NANOG. The patients' histopathologic diagnoses were based on the fourth edition of the *World Health Organization Classification of Tumours of Female Reproductive Organs*.[9] Immature teratomas were graded using a two-tiered system (low and high grade).[13] The tumors were staged using the International Federation of Gynecology and Obstetrics 2013 Ovarian Cancer Staging System.[14]

Immunohistochemical Staining

Immunohistochemical staining for SOX2 using the rabbit monoclonal antibody D6D9 (1:100 dilution; Cell Signaling Technology, Danvers, MA, USA), OCT4 using a rabbit polyclonal antibody (1:200 dilution; Cell Signaling Technology), and NANOG using the rabbit monoclonal antibody D73G4 (1:800 dilution; Cell Signaling Technology) was performed. After tumor sections were deparaffinized, rehydrated, and blocked using Peroxidazed 1 endogenous peroxidase blocker (PX968; Biocare Medical, Concord, CA, USA) at room temperature for 5 min, antigen retrieval was performed using Universal Decloaker buffer solution (UD1000M; Biocare Medical) in an autoclave at 125 °C for 30 s and 90 °C for 10 s. Nonspecific binding was blocked with Background Sniper blocking reagent (BS966M; Biocare Medical) for 30 min at room temperature. Slides were incubated with the primary antibodies overnight at 4 °C, a biotin-labeled secondary antibody (Universal Goat Link (GU600H); Biocare Medical) for 10 min, and 4plus HRP 1000 Universal Detection (HP604; Biocare Medical) for 10 min. After being stained with 3,3′-diaminobenzidine chromogen (DB801L; Biocare Medical), the sections were counterstained with hematoxylin, dehydrated, and mounted. Only nuclear staining for OCT4, NANOG, and SOX2 was considered to be positive.

Results

Clinical and Follow-Up Information

At the time of diagnosis of gliomatosis peritonei, the patients ranged in age from 5 to 42 years (mean, 22 years; median, 19 years). The clinicopathologic features of all cases were summarized in Table 1 and Table 2. Eight of the patients were white, eight were Hispanic, two were black, and one was Asian; information on race was not available for two patients. A total of 9 of 21 (43%) cases were consultation cases submitted by outside institutions. Seventeen patients had follow-up information and were alive with no evidence of disease ($n=13$), alive with disease according to restaging computed tomography (CT) scan ($n=3$), or alive with an unknown disease status ($n=1$). Their follow-up durations ranged from 1 to 229 months (mean, 49 months; median, 23 months). Four patients received chemotherapy before the diagnosis of gliomatosis peritonei (Table 2). Two of these four patients also developed growing teratoma syndrome (patient numbers 10 and 12), which was confirmed by CT scan (Table 2). One patient developed glioma arising from gliomatosis peritonei. She first presented with abdominal distention, weight loss, and ascites. Both CT scan and magnetic resonance imaging (MRI) showed a 29.0-cm pelvic mass. She underwent unilateral salpingo-oophorectomy, partial omentectomy, and was diagnosed with high-grade immature teratoma. Subsequently, patient received four cycles of etoposide and cisplatin chemotherapy. Follow-up CT and MRI showed sheet-like nodularity along the peritoneum and omental caking. She underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with cisplatin. A diagnosis of glioma arising from gliomatosis peritonei was made at that point. Patient received postoperative radiotherapy. She was alive with disease 4 months after the diagnosis of glioma (10 months after the diagnosis of ovarian immature teratoma).

Histopathology and Immunohistochemical Profiles

The primary ovarian neoplasms in this study were immature teratomas ($n=14$), mixed germ cell tumors with immature teratoma components ($n=6$), and a mature teratoma with a carcinoid tumor ($n=1$). Of the 14 immature teratomas, 5 were low grade, and 9 were high grade (Table 1). Eleven of 21 (52%) patients had metastatic immature teratoma ($n=4$), metastatic mature teratoma ($n=2$), or both ($n=5$). One patients had mature teratoma associated with a carcinoid tumor (case number 14).

Gliomatosis peritonei was diagnosed at the original surgery in 15 of 21 (71%) patients and at secondary surgery in 6 of 21 (29%) patients (Table 2). In addition, gliomatosis peritonei was diagnosed using H&E-stained slides in 15 of 21 (71%) cases, which were characterized by mature glial tissue in the peritoneum (Figure 1a and b). Gliomatosis peritonei formed individual nodules on the surface of the peritoneum or a mass-like lesion. Immunohistochemical staining for glial fibrillary acidic protein (GFAP) was performed in five cases, which demonstrated positive cytoplasmic staining, supporting the diagnosis of gliomatosis peritonei. Other immunohistochemical staining performed included that for S100 (positive in two cases), SALL4 (negative in one case), pan-cytokeratin (negative in one case), and CD99 (negative in one case).

Table 1 Clinicopathologic features of the 21 cases of gliomatosis peritonei

PT	*Age, years*	*Ovarian neoplasm*	*FIGO stage*[a]	*Metastatic immature teratoma*[b]	*Metastatic mature teratoma*[b]	*Lymph node status*	*GFAP*	*SOX2*	*OCT4*	*NANOG*	*Follow-up duration*[c]
1	18	Immature teratoma, low grade	IC2	No	No	Nodal gliomatosis	+	NA	NA	NA	ANED, 19 months
2	29	Immature teratoma, low grade	NA	No	No	NA	+	NA	NA	NA	ANED, 2 months
3	14	Immature teratoma, high grade	NA	Yes	No	NA	+	+	—	—	ANED, 92 months
4	15	Immature teratoma, low grade	NA	No	Yes	Mature teratoma	NA	+	NA	NA	NA
5	19	Immature teratoma, high grade	IA	No	Yes	Negative	NA	+	—	—	ANED, 58 months
6[d]	13	Mixed germ cell tumor	IA	No	No	Negative	NA	+	—	—	ANED, 71 month
7[d]	36	Mixed germ cell tumor	NA	Yes	Yes	NA	NA	NA	NA	NA	ADSU, 1 month
8	15	Immature teratoma, high grade	IA	No	No	NA	NA	+	—	—	ANED, 37 months
9	33	Immature teratoma, low grade	IA	No	No	NA	NA	NA	NA	NA	ANED, 184 months
10[d]	19	Mixed germ cell tumor	IIIC	Yes	Yes	Negative	NA	+	—	—	ANED, 46 months
11	22	Immature teratoma, high grade	IA	No	No	Negative	+	NA	NA	NA	ANED, 15 months
12[d,e]	40	Mixed germ cell tumor	IIIC	Yes	No	NA	NA	+	—	—	AWD, 29 months
13[d,e]	42	Mixed germ cell tumor	IIIC	Yes	Yes	Nodal gliomatosis	NA	+	—	—	AWD, 23 months
14	5	Mature cystic teratoma with carcinoid tumor	NA	No	No	NA	+	NA	NA	NA	ANED, 4 months
15[e,f]	10	Immature teratoma, high grade	NA	Yes	Yes	NA	NA	+	—	—	AWD, 10 months
16[d]	10	Mixed germ cell tumor	NA	No	No	Nodal gliomatosis	NA	NA	NA	NA	ANED, 11 months
17	21	Immature teratoma, high grade	NA	No	No	NA	NA	NA	NA	NA	NA
18	21	Immature teratoma, high grade	NA	Yes	No	Negative	NA	NA	NA	NA	NA
19	14	Immature teratoma, low grade	NA	No	No	NA	NA	NA	NA	NA	NA
20	22	Immature teratoma, high grade	NA	Yes	Yes	NA	NA	NA	NA	NA	ANED, 5 months
21	41	Immature teratoma, high grade	NA	Yes	No	IT	NA	NA	NA	NA	ANED, 229 months

Abbreviations: ADSU, alive, disease status unknown; ANED, alive with no evidence of disease; AWD, alive with disease; FIGO, International Federation of Gynecology and Obstetrics; GFAP, glial fibrillary acidic protein; NA, not available; PT, patient.

[a]International Federation of Gynecology and Obstetrics 2013 Ovarian Cancer Staging System.

[b]Identified at a different anatomic site from that of gliomatosis peritonei.

[c]Duration of follow-up after the diagnosis of primary ovarian neoplasms. Updated on June 2015.

[d]Mixed germ cell tumors were composed of immature teratoma and yolk sac tumor in case numbers 6, 13, and 16, and were composed of immature teratoma, yolk sac tumor, and embryonal carcinoma in case numbers 7, 10, and 12.

[e]These three patients were alive with disease according to the follow-up/restaging computed tomography (CT) scan: patient number 12 had diffuse peritoneal disease in the subdiaphragmatic regions bilaterally, involving the surfaces of the liver and spleen; patient number 13 had multiple peritoneal deposits (the largest measuring 5.0 cm in greatest dimension); patient number 15 had a mass within the cul-de-sac (~6.0 cm).

[f]Patient developed glioma arising from gliomatosis peritonei.

Table 2 Summary of six cases that gliomatosis peritonei was diagnosed at secondary surgeries

PT	*Peritoneal findings at first surgery*	*Additional biopsies after first surgery*[a]	*Peritoneal findings at the same time as GP*	*Interval between first and second surgeries (months)*	*Reason for second surgery*	*Chemotherapy before second surgery*	*Chemoradiation after second surgery*	*Follow-up duration after diagnosis of GP or glioma*[b]	*Additional findings*
3[c]	NA	IT	GP	24	Disease progression[d]	Yes, BEP and more[d]	Radiation	ANED, 68 months	NA
9	NA	NA	GP	182	Abdominal and pelvic pain[e]	No	No	ANED, 1.5 months	NA
10[c]	IT, MT	MT (liver mass)	GP, MT	10	Residual masses (CT)	Yes, BEP 6 cycles	No	ANED, 36 months	GTS[f]
11	NA	NA	GP	4	FDG-avid lesion (PET-CT)	No	No	ANED, 11 months	Encephalitis[g]
12[c]	IT	NA	GP	4	Peritoneal thickening (CT)	Yes, BEP 3 cycles	Yes, interferon	AWD, 25 months	GTS[h]
15[c]	IT	NA	GP, glioma, IT, MT	6	Sheet-like nodularity along the peritoneum and omental cake (CT and MRI)	Yes, EP/PE 4 cycles	Yes, HIPEC and radiation	AWD, 4 months	NA

Abbreviations: ADSU, alive disease status unknown; ANED, alive with no evidence of disease; AWD, alive with disease; BEP, bleomycin, etoposide, cisplatin; CT, computed tomography; EP/PE, etoposide and cisplatin chemotherapy; FDG, fludeoxyglucose F 18; GP, gliomatosis peritonei; GTS, growing teratoma syndrome; HIPEC, hyperthermic intraperitoneal chemotherapy; IT, immature teratoma; MRI, magnetic resonance imaging; MT, mature teratoma; NA, not available; PET, positron emission tomography; PT, patient.

[a]Biopsies performed after the first surgery, but before the diagnosis of GP.

[b]Please refer to Table 1 for the follow-up duration after diagnosis of primary ovarian neoplasms.

[c]Patient numbers 3, 10, 12, and 15 had ascites. However, time course of development of ascites suggested its association with either primary ovarian neoplasm or metastatic immature teratoma.

[d]Because patient had disease progression while on BEP, she also received paclitaxel, ifosfamide, and cisplatin for three courses.

[e]It was unclear whether abdominal and pelvic pain was associated with gliomatosis peritonei or endometriosis. The patient was previously diagnosed with endometriosis clinically, but it was never confirmed by pathology. Endometriosis was not present in all available pathology specimen.

[f]Patient developed growing teratoma syndrome after chemotherapy, and had multiple masses in the abdomen and pelvis. Biopsy of 7.5-cm liver mass showed mature teratoma.

[g]Patient developed anti-NMDA receptor encephalitis.

[h]After the secondary surgery, patient was diagnosed as growing teratoma syndrome. Follow-up CT scan showed bilateral subdiaphragmatic implants encasing the liver and spleen, and pelvic implants encasing the uterus and sigmoid colon.

To determine the stem cell origin of gliomatosis peritonei, we performed immunohistochemical staining for OCT4, NANOG, and SOX2 in sections containing gliomatosis peritonei. The results demonstrated that SOX2 (Figure 1c and d) was diffusely expressed in nine of nine cases (100%) with either available tissue blocks or unstained slides, whereas OCT4 (Figure 1e) and NANOG (Figure 1f) were not expressed in eight of eight cases with tissue blocks.

One patient developed glioma arising in the setting of gliomatosis peritonei. Tissue sections demonstrated extensive gliomatosis with foci of increased cellularity and nuclear atypia (Figure 2a), abundant mitotic figures with a manual mitotic count revealed 5–7 mitotic figures per 10 high-power fields (Figure 2b), vascular proliferation (Figure 2c), and necrosis (Figure 2d). Quantitative assessment of immunohistochemical staining for Ki-67 (Figure 2e) showed average proliferation index of 22.2% and quantitative assessment of immunohistochemical staining for phosphohistone H3 revealed 2.3 mitotic figures per 1000 total nuclei, supporting a diagnosis of high-grade glioma, similar to glioblastoma multiforme (grade IV) from central nervous system. Immunohistochemical staining of specimens of glioma demonstrated that the tumor cells were positive for SOX2 (Figure 2f) but negative for OCT4 and NANOG. Moreover, next-generation sequencing-based analysis of this case of glioma failed to identify any mutations in the coding sequences of 50 genes, including *BRAF*, *PIK3CA*, *PTEN*, *IDH1*, and *IDH2*.

Discussion

In this study, we examined the clinicopathologic and immunohistochemical features of gliomatosis peritonei in one of the largest reported series of such patients in the literature. Gliomatosis peritonei was diagnosed at the same time as primary ovarian neoplasms in the majority of the patients (71%). Approximately half of the patients also had metastatic immature teratoma, metastatic mature teratoma, or both. Although gliomatosis peritonei was often diagnosed on H&E-stained tissue sections, inflammatory cell infiltration, hemorrhage, and choroid plexus can be seen in patients with gliomatosis peritonei, which makes it a diagnostic challenge. Differentiating choroid plexus from low-grade epithelial ovarian tumors may be difficult, especially on intraoperative frozen sections. In these challenging situations, immunohistochemical staining for GFAP may be helpful.

Clinically, gliomatosis peritonei is considered grade 0 teratoma and is usually associated with favorable prognosis and managed conservatively, which is supported by our present findings. However, several conditions must be considered before such a diagnosis is made: First, one must consider the coexistence of metastatic immature and/or

mature teratoma before making such a diagnosis. Therefore, carefully examining all specimens is important, as the presence of metastatic immature teratoma affects prognosis and alters the treatment course. Second, on rare occasions, malignant transformation of glioma should be also considered as

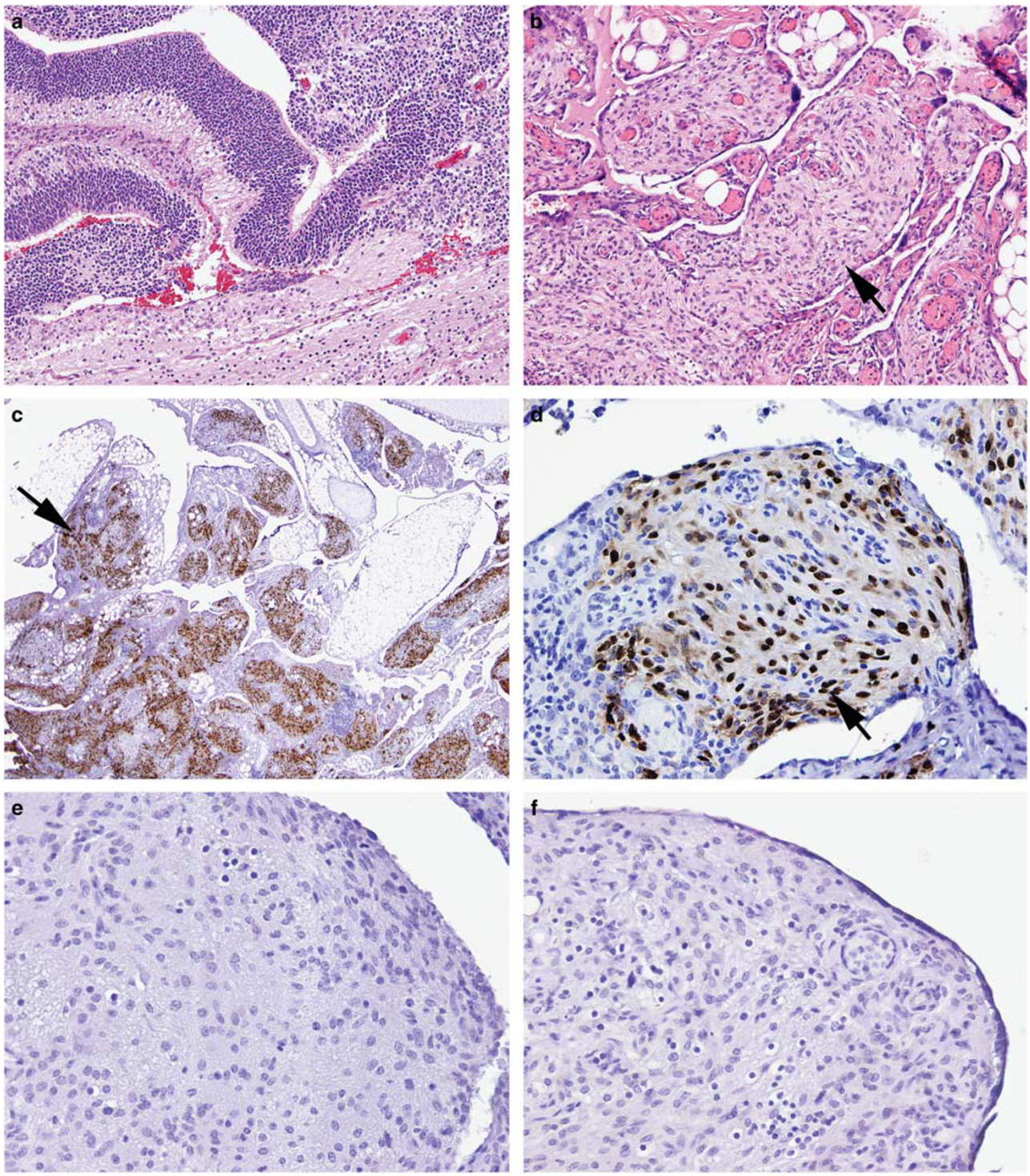

Figure 1 Staining of gliomatosis peritonei specimens for OCT4, NANOG, and SOX2. (**a**) Patient's ovarian mass was a mixed germ cell tumor, predominantly composed of immature teratoma (hematoxylin and eosin stain; original magnification, ×100). (**b**) Mature glial tissue in the peritoneal cavity demonstrated a micronodular growth pattern, consistent with gliomatosis peritonei (hematoxylin and eosin stain; original magnification, ×100). (**c** and **d**) Glial cells demonstrated strong, diffuse nuclear staining for SOX2 (immunohistochemical stain; original magnification, ×20 and ×200 in **c** and **d**, respectively). (**e**) Glial cells were negative for OCT4 (immunohistochemical stain; original magnification, ×200). (**f**) Glial cells were negative for NANOG (immunohistochemical stain; original magnification, ×200).

described here and by other authors.[11,12] Third, gliomatosis peritonei can be part of growing teratoma syndrome, characterized by increasing growth of metastatic mass that is composed of mature teratoma especially in patients who have received chemotherapy for malignant germ cell tumor.[15–20]

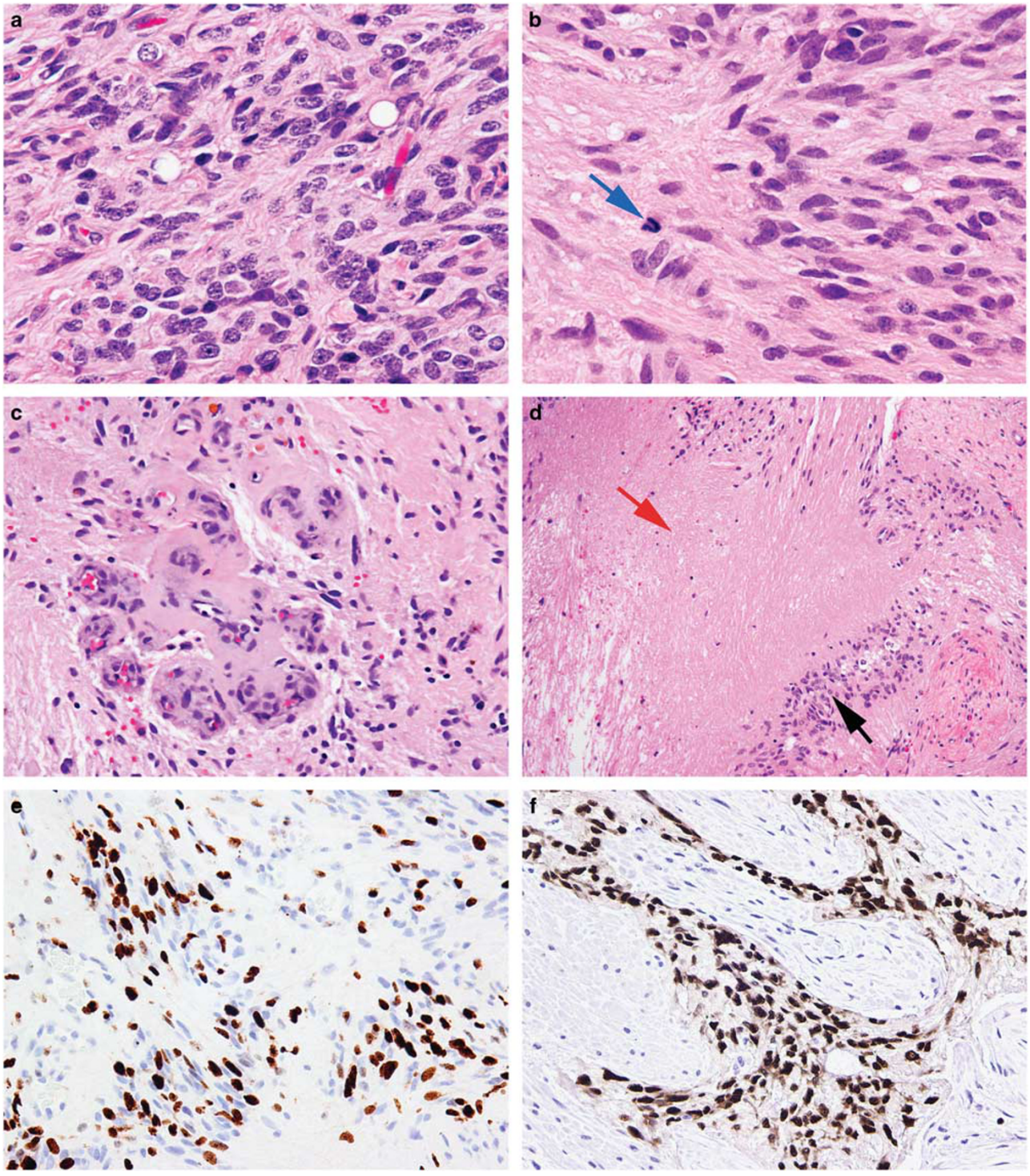

Figure 2 Staining of a specimen of glioma arising from gliomatosis peritonei. (**a** and **b**) Glioma cells showed increased nuclear atypia and mitotic figures (blue arrow; hematoxylin and eosin stain; original magnification, ×400). (**c**) Vascular proliferation (hematoxylin and eosin stain; original magnification, ×200). (**d**) Glioma cells (black arrow) and necrosis (red arrow; hematoxylin and eosin stain; original magnification, ×100). (**e**) Ki-67 immunohistochemical staining demonstrated high proliferative index of glioma (immunohistochemical stain; original magnification, ×200). (**f**) Glioma cells demonstrated positive nuclear staining for SOX2 (immunohistochemical stain; original magnification, ×200).

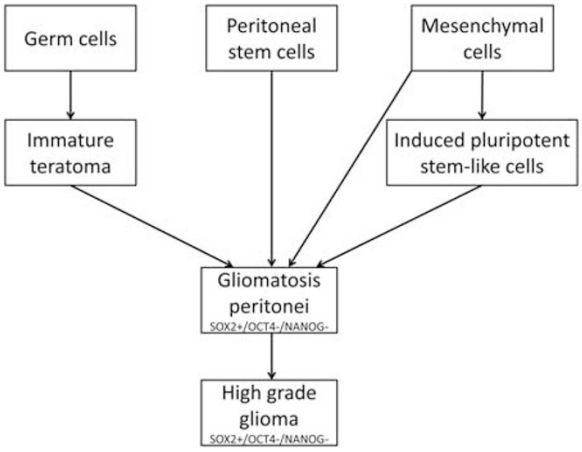

Figure 3 Hypotheses regarding the origin of gliomatosis peritonei. First, it may derive from an immature teratoma that undergoes maturation or from cancer stem cells within an immature teratoma. Second, it may derive from peritoneal stem cells that differentiate toward the neural lineage induced by factors secreted by teratoma. Third, it may derive from subperitoneal mesenchymal cells that transdifferentiate into glial cells either directly or through an intermediate stage of induced pluripotent stem-like cells.

Our results demonstrated that the tumor cells in gliomatosis peritonei specimens expressed SOX2 but not OCT4 or NANOG in all cases with tissue blocks or unstained slides available for immunohistochemical staining, which provides an important molecular clue on the origin of this disease. This is in keeping with the findings reported by Nogales *et al.*[21] SOX2 is one of the key factors for maintenance of pluripotency in stem cells[22,23] and its expression is required for inducing stem cells to differentiate toward the neural lineage.[24,25] SOX2 is expressed in neural stem cells,[26] in the majority of glial tumors,[27] in immature teratoma cases,[26] and in epithelium of endodermal origin in mature teratoma cases.[26] Several hypotheses regarding the origin of gliomatosis peritonei have been proposed in the literature (Figure 3), including germ cell origin, as it is frequently associated with germ cell tumors, peritoneal stem cells that differentiate into glial cells under the stimulation of factors secreted by teratomas[21,28] or transdifferentiation from subperitoneal mesenchymal cells or via induced pluripotent stem-like cells into glial cells.[29,30] Taken together, our data together with other investigators' finding support a key role for SOX2 in the pathogenesis of gliomatosis peritonei, although detailed mechanisms of how SOX2 induces gliomatosis via one or combinations of three mechanisms mentioned above remains to be determined.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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