Exploring the role of SOX 2 and OCT 4 in the pathogenesis of gliomatosis peritonei: the clinicopathological profile of eleven cases

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Abstract

Objective: Gliomatosis peritonei (GP) is a rare entity characterized by multiple mature glial tissue implants in association with ovarian teratomas in the peritoneum and omentum. To date, only 100 cases have been published. Not much is known about the origin, clinicopathological profile or prognosis of GP. SOX2 and OCT4 are recently recognized markers of embryonic stem cell differentiation. Here, the role of SOX2 and OCT4 in the pathogenesis of 11 cases of GP are reported and clinicopathological factors are described.

Material and Methods: This was a retrospective study of six years duration (2017-2022). All the cases of GP were retrieved from archives, the diagnosis was confirmed and clinicopathological factors were noted. Immunohistochemical (IHC) investigation for glial fibrillary acid protein (GFAP) and S100 was noted wherever available. IHC for SOX2 and OCT4 was performed using an avidin-biotin technique.

Results: There were 11 cases of GP identified. The median age was 29 years and 1/11 cases had nodal gliomatosis as well. There were eight cases of immature teratoma and three cases of mature cystic teratoma. SOX2 was positive in all foci of GP, while OCT4 was negative. These foci were also positive for GFAP and S100.

Conclusion: A possibility of GP should be considered as a differential, clinically and radiologically, in cases of omental nodularity. Adequate sampling at the time of surgery is essential to rule out metastasis or growing teratoma syndrome. SOX2, a stem cell marker inducing neural differentiation, may play a crucial role in the development of GP in association with other transcription factors. (J Turk Ger Gynecol Assoc 2024; 25: 66-73)

Keywords: Ovary neoplasm, teratoma, gliomatosis peritonei, SOX2, omental glial implants, malignant transformation, mature cystic teratoma, growing teratoma syndrome

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Introduction

Gliomatosis peritonei (GP) is a rare entity characterized by multiple mature glial implants in the peritoneum and omentum. It is associated with teratomas, usually immature teratoma (IMT), in most of cases. To date only 100 cases have been reported (1). According to the World Health Organization (WHO) guidelines for grading IMT, this tumor is graded as grade 0 and is thought to have good prognosis wherever found. However, due to the rarity of this disease, there is little data pertaining to its clinicopathological characteristics. Moreover, the origin of GP is still ambiguous. Recent studies of stem cell differentiation have demonstrated that OCT4 (Pou5f1-POU domain, class 5, transcription factor 1) and SOX2 (SRY-box containing gene 2), in conjunction with other transcription factors, act as master regulators for embryonic stem cell differentiation towards mesoderm (2). Several authors have demonstrated that SOX2 plays a key role in direct reprogramming of human somatic cells into neural progenitor cell types (3). In this study, 11 cases of GP diagnosed and treated at our referral center were retrospectively reviewed

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and the role of SOX2 and OCT4 was investigated in these cases. The currently published literature was also reviewed to add to the understanding of this rare disease.

Material and Methods

Clinical Profile

This was a retrospective study of all cases of GP received at our referral centre in India. Over the last 6 years (2017-2022), 11 cases of GP were identified. The clinical and pathological details of these cases were retrieved from the records and retrospectively reviewed to evaluate the clinicopathological factors, including age, laterality, serum markers, radiological details, nature of primary tumor, morphological features, and complications, if any. The outcomes were noted where available. Cases where sufficient details or histopathology slides were not available were not included in the study. For the purpose of this study, cases where GP was associated with growing teratoma syndrome (GTS), or with a history of prior chemotherapy were excluded. Since this study was performed on retained histopathological samples from the departmental archives, ethics approval was not taken as per our institutional review board guidelines. Descriptive statistics was used and the results were expressed as percentages. Data was analyzed using SPSS software, version 22, wherever needed (IBM Inc., Armonk, NY, USA).

Pathological Profile

Histopathological slides of all cases were reviewed by two pathologists for confirmation of diagnosis of the primary tumor, the amount of mature glial differentiation in the primary tumor (all teratomas), the grade of IMT, stage, presence of metastatic disease and the extent of GP was noted. IMTs were graded as per the published guidelines. All the lymph node slides were reviewed to look for presence of nodal gliomatosis and to exclude coexisting nodal metastasis.

Immunohistochemical Staining

Immunohistochemistry (IHC) for glial fibrillary acid protein (GFAP) and S100 was noted from the records (done as a part of routine diagnostic workup). Paraffin-embedded tissue blocks (n=11) and an unstained, Poly-L-Lysine coated slide, containing GP were used for IHC staining for SOX2 and OCT4. IHC staining for SOX2, using the human monoclonal antibody at 1:100 dilution and pH 9 (Zeta corporation) and OCT4, using a monoclonal antibody at 1:100 dilution and pH6 (Zeta corporation) was performed. The tumor sections were deparaffinized, rehydrated, blocked with endogenous peroxidase blocker at room temperature for five minutes and antigen retrieval was performed using the microwave method. Slides were incubated with primary antibodies overnight at 4 °C, followed by a biotin-labelled secondary antibody for 10 minutes. Following staining with 3,3'-diaminobenzidine chromogen, the sections were counterstained with haematoxylin, dehydrated, and mounted. Appropriate positive controls and negative controls were included in each run. Only nuclear staining for OCT4 and SOX2 was considered to be positive.

Statistical analysis

Descriptive statistics were produced using SPSS, version 22 (IBM Inc., Armonk, NY, USA) and results were calculated as percentages in this study.

Results

A total of 615 ovarian teratomas (OT) were received in the department of pathology in the last six years, of which 472 were mature cystic teratomas (MCT) and 143 were IMT. Only 1.6% (11/615) of all teratomas were associated with GP. One of the patients having GTS with GP was excluded from this study. The clinicopathological details of these 11 patients are summarized in Table 1 and the histopathology review findings are summarized in Table 2. Nearly all the patients presented with a short history (average 1.5 months) of abdominal distention along with complaints of abdominal pain in some. The median (range) age of GP patients was 29 (14-35) years and the median size of primary ovarian tumor was 21.4 (14-29) cm. The tumor was left sided in 6/11 cases, right sided in three and was bilateral in two. The serum CA125 levels, available for four cases, was raised, ranging from 324 to 906 U/mL. While radiological investigations in all cases diagnosed adnexal mass with accuracy, the associated GP nodules were reported as peritoneal/omental deposits or thickening and were misperceived as peritoneal carcinomatosis in 50%, more so with IMT cases.

Grossly, the adnexal masses were predominantly solid cystic with areas of hemorrhage and necrosis in IMT. The omental nodules ranged in size from 0.3 to 0.8 cm in diameter and were grey, and white and homogenous on cut section. On microscopy, a total of 11 teratoma cases were associated with GP, 8/11 of these were IMT and the rest (4/11) were MCT. Of the IMT, 71% (6/8) were grade 3 and 2/8 were grade 2. We did not find any case of low grade IMT (grade 1) associated with GP in this series. Of the four MCTs, one was bilateral in origin, and one coexisted with IMT in the other ovary. Table 2 summarizes the histopathological findings of these cases. It was noted that in all cases, the extent of mature glial differentiation accounted for up to 20% of the primary tumor on average, ranging from 5-45%. Case 5 with bilateral MCT had mature glia in both the tumors, although the one on the left side showed up to 45% of mature glial differentiation with no capsular breach, while the right side exhibited only 15%. Case 11 also showed mature

glial tissue in both ovaries. Capsular breach was noted in 63% (7/11) of cases, including one case of MCT (Case 2). Along with capsular breach, Case 2 also had nodal GP but had no recurrence or metastasis on follow-up. IHC staining for GFAP and S100 as a part of routine diagnostic workup was performed in six cases, all of which demonstrated positive cytoplasmic staining, supporting the diagnosis of GP. Other IHC stains performed included SALL4, pan-cytokeratin and CD99 in Case 6 which were immunonegative on IHC.

IHC for SOX2 and OCT4 was performed to investigate the stem cell origin of GP foci in these cases. It was noted that while 100% (11/11) of these cases showed diffuse nuclear immunopositivity for SOX 2, all were immunonegative for OCT 4 (Figure 1).

Table 1. Clinicopathological features of 11 cases of GP

Case no.	Age	Cl/F	CA125, U/mL	Site	Tm size	Procedure	Diagnosis	Mets/Om	Outcome
1	22	AD*, PA# x 1 m	392	Rt	20	RSO, Om, PLND	IMT grade 3	GP	Alive; 60 months
2	27	AD*, PA# x 2 m	NA	Lt	23	TAH + BSO, Om, PLND, peritonectomy	MCT	GP with nodal GP	Alive at 48 months
3	32	AD* x 3 m	NA	Lt	25	LSO, peritonectomy	IMT grade 3	GP	Alive; 46 months
4	31	AD* x 1 m	367	Rt	23	RSO, Om, POD bx	IMT grade 2	GP	Alive; 38 months
5	23	AD*, PA# x 1 m	324	B/L	20	LSO, Rt cystectomy, Om, peritoneal Bx	B/L MCT	GP	Alive; 24 months
6	30	AD* x 2 m	238	Lt	19	LSO, Om	IMT grade 2	GP	LTFU
7	35	PA#, AD* x 1 yr	NA	Rt	29	TAH, BSO, Om	MCT	GP	Alive; 15 months
8	34	AD* x 3 m	NA	Lt	14	TAH BSO, Om	IMT grade 3	GP	LTFU
9	27	AD* x 1 m	906	Lt	17	LSO, Om, peritoneal Bx	IMT grade 3	GP	Alive; 14 months
10	14	AD*, PA# x 1 m	NA	Lt	24	LSO, Om, peritoneal Bx	IMT grade 3	GP	Alive; 6 months
11	30	AD* x 3 m	NA	Rt	24	RSO, Lt cystectomy, Om	IMTgrade 3 Rt MCT Lt	GP	Alive at 3 months

*AD: Abdominal distention, #PA: Pain abdomen, IMT: Immature teratoma, MCT: Mature cystic teratomas, GP: Gliomatosis peritonei, Rt: Right, Lt: Left, Om: Omentectomy, RSO: Right salpingoophrectomy, LSO: Left salpingoophorectomy, TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-ophrectomy, POD: Pouch of douglas, B/L: Bilateral, PLND: Peritoneal Lymph node dissection, LTFU: Lost to follow-up

Table 2. Histopathological findings in 11 cases of GP

Case	Diagnosis	Grade	Morphology (%) of mature glia in the tumor	Capsular breach	Metastasis	IHC GFAP	IHC S100	IHC SOX2	IHC OCT4
1	IMT	3	10-20%	No	No	NA	NA	+	-
2	MCT		20-30%	+	No	+	NA	+	-
3	IMT	3	10-20%	+	No	+	NA	+	-
4	IMT	2	30-35%	+	No	+	+	+	-
5	B/L MCT		40-45% in Lt and 5-10% in Rt	No	No	+	NA	+	-
6	IMT	2	20-25%	+	No	NA	+	+	-
7	MCT		5-10%	No	No	NA	+	+	-
8	IMT	3	20-25%	+	No	+	+	+	-
9	IMT	3	20-25%	+	No	NA	+	+	-
10	IMT	3	15-20%	+	No	+	+	+	-
11	IMT Rt MCT Lt	3	20-25% in Rt and 10-15% in Lt	No	No	NA	NA	+	-

GP: Gliomatosis peritonei, IHC: Immunohistochemical, GFAP: Glial fibrillary acid protein, IMT: Immature teratoma, MCT: Mature cystic teratomas, B/L: Bilateral, Rt: Right, Lt: Left

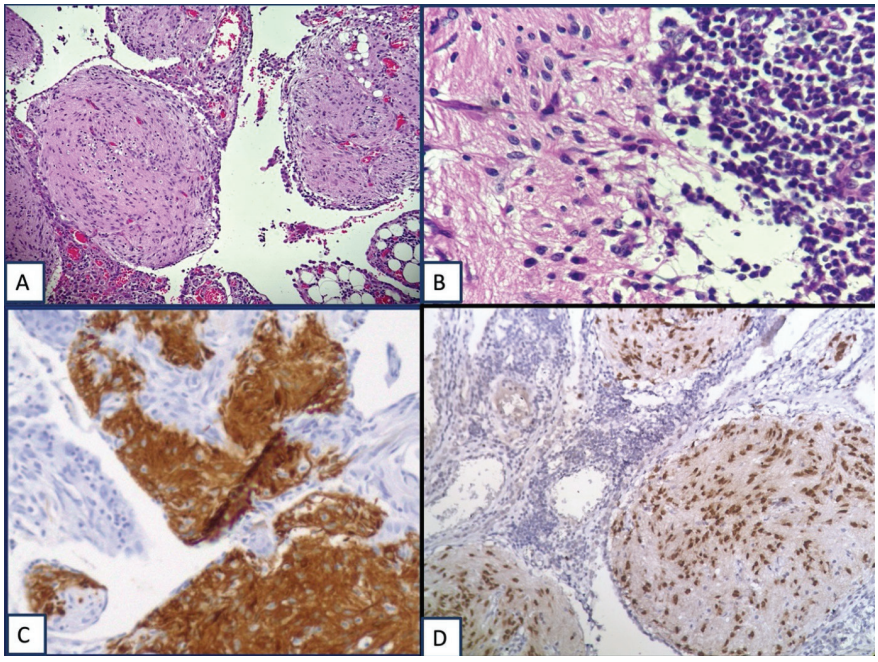

Figure 1. H&E-stained images of foci of GP (A) and nodal GP (B) along with IHC of GFAP (C) and SOX2 on GP foci (D)
H&E: Hematoxylin and eosin, GP: Gliomatosis peritonei, IHC: Immunohistochemical, GFAP: Glial fibrillary acid protein

Table 3. Summary of case series of GP published to date

	Study	Number of cases	Median age (years)	Size (cm)	Ovarian Tm	Diagnosis	Nodal GP	Treatment	Recurrence/ metastasis	Follow-up
1	Wang et al. (1), (2016)	8	20	20.4	IMT: G1: 2, G2-G3: 5, MCT: 1	1st surgery: 6, 2nd surgery: 2	4 (IMT1, MCT 1)	S: 3, S + Ch: 5	No	Alive: 8
2	Liang et al. (4), (2015)	14	NA	NA	IMT: G1: 5, G2-G3: 9	1st surgery: 10, 2nd surgery: 4	3 (IMT1, MCT2)	NA	NA	Alive: 10, NA: 4
3	Bentivegna et al. (5), (2015)	9	36	NA	IMT: G1: 5, G2-G3: 4	1st surgery: 1, 2nd surgery: 8	NA	S: 5, S + Ch: 4	22.2%, (2/9)	Alive: 9
4	Yoon et al. (6), (2012)	16	15	19.8	IMT: G1: 4, G2-G3: 11, MCT:1	1st surgery: 15, 2nd surgery: 1	NA	S: 3, S + Ch: 13	37.5%, (6/16)	Alive: 15, Dead: 1
5	Harms et al. (7), (1989)*	13	11.5	14	IMT: G1:8, G2-G3: 5	1st surgery: 11, 2nd surgery: 2	1 (IMT)	S: 6, S + Ch: 7	No	13
6	Norris et al. (8), (1976)	7	15	25	IMT: G1: 5, G2-G3: 4	1st surgery: 9	NA	S: 4, S + Ch: 1, S + Rx: 2	NA	Alive: 5, Dead: 1, NA: 1
7	Present study	11	29	21.4	IMT: G2-G3: 8, MCT: 3	1st surgery: 11	1 (MCT)	S: 3, S + Ch: 8	No	Alive: 9, NA: 2
	Total	78	NA	NA	IMT G1: 27, G2-G3: 45, MCT: 5	1st surgery: 60, 2nd surgery: 17		S: 24, S + Ch: 37, S + Rx: 2: NA: 14	14.2% (8/56)#	Alive: 68, Dead: 2, NA: 7

*Study was conducted in children and adolescent age group, #Cases with no data on recurrence were not included, GP: Gliomatosis peritonei, IMT: Immature teratoma, MCT: Mature cystic teratomas, S: Surgery, Ch: Chemotherapy, NA: Not available, Rx: Radiotherapy

In these cases 7/10 underwent unilateral salpingo-oophorectomy, along with comprehensive staging surgery. The diagnosis of GP was made after primary surgery in all the cases in our study. Three patients underwent total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) along with omentectomy, peritoneal lymph node dissection (PLND) and multiple biopsies from various sites. While one of these patients (Case 8) was 34 years of age with a huge adnexal mass of 29 cm, the other (Case 2) was 27 years of age with extensive disease. These patients were diagnosed as IMT on radiology and had multiple deposits spread extensively over the omentum, peritoneum, rectal wall, and bladder wall. Since the exact nature of these deposits was not discernible by radiology alone, a TAH with BSO along with omentectomy and PLND was preferred in these cases. On reviewing all the 10 cases where PLND was performed, all cases were free from metastatic disease and only one had nodal gliomatosis.

As per the NCCN guidelines, patients with IMT having grade 2/3 disease were treated with postsurgical chemotherapy, while those with MCT were treated with surgery alone. The mean follow-up period was 33 months. In terms of outcome, 9/11 patients are alive with no evidence of recurrence or metastasis and two were lost to follow-up.

Discussion

The presence of mature glial tissue implants in the peritoneal cavity is termed GP. It is important to note that these glial implants when benign are graded as grade 0 by the fifth edition of WHO. Since these are found as nodules of varying sizes in the peritoneal cavity they are often misdiagnosed as metastasis or tuberculosis clinically and radiologically (1). The mean age of patients in the present series was 29 years, which was comparable to previous reports in adults, with the exception of Harms et al. (7) who studied the incidence of GP in the child and adolescent age group and found a mean age of 13 years. The mean size of main adnexal mass at 21 cm was also comparable to earlier studies (1).

To date, only 100 cases of GP have been published. A comprehensive literature search identified only six case series that included more than five cases for analysis (1,4-8). Table 3 summarizes the clinicopathological features of GP case studies published to date. Most of these cases have been reported with teratoma of the ovary, though a few cases of mixed germ cell tumors (MGCT) or GTS have also been reported (1,4-9). Of the total of 106 cases of GP, including published case series and various case reports and the present series, we found that only nine cases were associated with MCT and rest were mostly IMT, with five cases of MGCT (1). We did not include cases associated with GTS, as the true nature of these implants is still controversial. The incidence of GP associated with MCT was, however, highest in the present study compared to other studies [36%, 4/11 cases] (4,7,8). One of our cases was a bilateral MCT associated with GP. Yoon et al. (6) reported 15/16 cases of IMT associated with GP, and of these, four were low grade while 11 were high grade. In the present study all IMT were high grade. The largest study of 21 cases, reported by Liang et al. (4), reported 14 cases of IMT, six cases of MGCT and only one case of MCT associated with GP. There were no cases of MGCT with GP in our archives.

Though the exact etiology of GP is still unknown, two main hypotheses related to its origin have been proposed (8,10). The first largely relates to the presence of capsular breach in the primary teratoma, leading to the development of mature glial implants. This hypothesis also includes the possibility of lymphovascular spread of mature glial tissue, as is evident from nodal gliomatosis found in the literature. We found capsular breach in 7/10 of our cases, including six IMT and one MCT. Robboy and Scully (11) reported similar findings in 11 of 12 cases in their report. Kim et al. (12) reviewed 100 cases of

Table 4. Summary of cases showing LN gliomatosis in the literature and the present study

Author and year	Journal	Age	LN sites	Primary tumor	Treatment	Prognosis
Liang et al. (4), (2015)	Mod. pathology	18	LN	IMT - G1	NA	Alive at 19 months
		42	LN	MGCT	NA	Alive at 23 months
		20	LN	MGCT	NA	Alive at 11 months
Wang et al. (1), (2016)	Journal of Ovarian Research	25	Iliac	MCT	S	Alive 3 months
		16	Iliac	IMT G2	S + Ch	Alive 68 months
		22	Iliac	IMT G1	S + Ch	Alive 60 months
		17	Iliac	IMT G3	S + Ch	Alive 144 months
Kim et al. (12) (2013)	Korean Journal of Pathology	34	Hypogastric	IMT G1	S	Alive at 9 months

Table 4. Continued

Author and year	Journal	Age	LN sites	Primary tumor	Treatment	Prognosis
Fang et al. (13), (2015)	Zhonghua Bing Li Xue Za Zh	20	Paraaortic	IMT G3	S + Ch	Alive at 36 months
Chou et al. (14), (2005)	Taiwanese J of Obstet Gynecol	36	Omental	MCT	S	Alive at 12 months
Khan et al. (15), (2005)	Gynecol Oncol	23	LN	IMT G1	S + Ch	NA
Perrone et al. (16), (1986)	Arch Pathol Lab Med	10 months	Paraaortic	IMT G1	S	Alive at 9 months
El Shafie et al. (17), (1984)	J Surg Oncol	12 years	Omental	MCT	S	Alive at 5 years
Nagashima et al. (18), (1974)	Acta Pathol Jpn	22	Inguinal, mesenteric, mediastinal, cervical	IMT	S + Ch	Dead at 8 months
Benirschke et al. (19), 1960	Obstet Gynecol	18	Retroperitoneal, iliac, cervical axillary	MCT	Ch + radiotherapy	Dead at 8 months
Alna'irat et al. (20), (2023)	Int J Gynecol Pathol	23	Pelvic LN	IMT	S + Ch	Alive
Present study (2023)		27	Pelvic and omental	MCT	S	Alive at 48 months

LN: Lymph node, IMT: Immature teratoma, MCT: Mature cystic teratomas, MGCT: Mixed germ cell tumors, S: Surgery, Ch: Chemotherapy, NA: Not available, Mod. pathology: Modern pathology

GP and found nine cases with nodal gliomatosis in pelvic or para-aortic LN. Three of these cases were, however, not true nodal GP, as they had teratomatous components along with glial implants. In 2016, Wang et al. (1) reported eight cases with GP, of which three had nodal GP. Recently, Alna'irat et al. (20) reported a case of nodal GP with ITM in a young girl and reviewed the literature on nodal GP. In their review they also explained nodal GP on the basis of metaplasia of nodal mesothelial cells, secondary to factors secreted by the primary ovarian neoplasm. Table 4 summarizes the cases showing nodal gliomatosis from the reviewed literature. There were 17 cases of nodal gliomatosis, of which five were associated with MCT (including the case presented here), 10 with IMT and two were MGCT (1,4,12-20). Moreover, the occurrence of GP following ventricular-pontine shunts, as reported by Lobotesis et al. (21), also favoured this theory.

In the search for the pathogenesis of GP, Ferguson et al. (22), in 2001, used polymorphic microsatellite (MS) in two cases of GP and found that, like normal tissue, GP foci were also heterozygous while the teratoma cells were homozygous for MS loci (19). This supports the second hypothesis concerning the origin of GP, which suggests that glial foci are genetically not associated with teratoma and instead arise from metaplasia of normal cells, such as peritoneal cells or pluripotent Mullerian stem cells (22). Cases reported by Bässler et al. (23), Killeen et al. (24) and the study conducted by Kim et al. (12) where GP was found to coexist with endometriosis, further supports this metaplasia hypothesis (25). The authors also believed that the teratomas may secrete some factors that stimulates glial differentiation affecting not only peritoneal stem cells but also leading to glial differentiation in the tumor itself. In all our cases of teratoma associated with GP, we found an average of 20% mature glial differentiation (range; 5-45%) in the main tumour. Liang et al. (4) performed IHC for SOX2, OCT4 and NANOG in nine cases of GP. In accordance with their observation, all our cases were also positive for SOX2 and immunonegative for OCT4, indicating that SOX2 may have an important role in the development of GP. The observation of Nogales et al. (26) that SOX2 plays a major role in maintaining pluripotency of stem cell and that of Maucksch et al. (27) establishing the key role of SOX2 in inducing stem cells towards neural differentiation, further supports the metaplastic hypothesis. Moreover, SOX2 is also expressed in neural stem cells, IMTs, endodermal derivatives of mature teratomas and glial tumors, suggesting that SOX2 may lead to the development of GP in association with other transcription factors (28). Figure 2 summarizes the various hypotheses pertaining to the pathogenesis of GP. However, since GP is such a rare condition, the exact mechanism leading to the development of glial follicles in the peritoneum still needs to be discerned.

The first is that it may arise from cancer stem cells within IMTs or from IMTs that may have undergone maturation. The second hypothesis supports the development of GP from peritoneal stem cells that differentiate towards a neural lineage, as induced by various factors secreted by teratomas. The third hypothesis suggests that GP may actually derive from subperitoneal

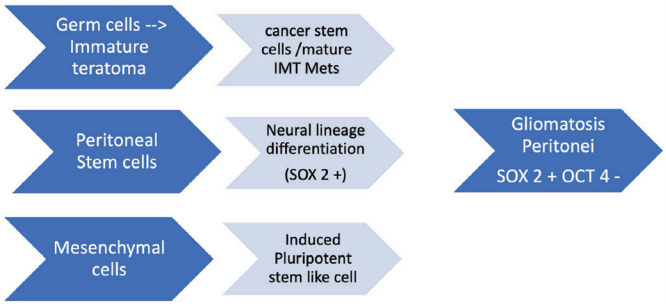

Figure 2. Summary of hypotheses concerning the pathogenesis of gliomatosis peritonei

mesenchymal stem cells that either directly transdifferentiate into glial cells or are converted to an induced pluripotent stem, as in cell forming mature glial nodules.

While MCT are managed by surgery alone (cystectomy/salpingo-oophorectomy), IMT stage 1 and grade 1 are managed by surgery (fertility sparing surgery with comprehensive staging, if desirable of fertility or a completion staging surgery if fertility is not desired) followed by observation, as per published Guidelines. High grade IMT (grade 2 or 3) or stage 2 and above diseases, on the other hand, are treated with surgery and a chemotherapy regimen. All cases in our study were high grade IMT (7/10), and thus were treated with surgery followed by chemotherapy. In the literature review, out of a total of 77 cases of OT with GP, 24 patients were treated with surgery and 37 patients were treated with both surgery and chemotherapy. Prognosis in these cases depended predominantly on the stage and grade of the primary tumor and on the grade of its metastatic tumor deposits.

In 1970, when Robboy and Scully (11) reviewed 12 cases of OT with glial implants, they concluded that the prognosis of OT or metastasized OT was favorable when associated with mature glial tissue implants. However, later in 2002, Müller et al. (25) reported 11 cases of GP with adverse outcomes. It was reported that in all these cases, adverse outcome was attributable to lack of histological sampling at the time of first surgery. It is thus advisable to take multiple biopsies and perform adequate sampling at the time of first surgery to rule out immature glial/teratoma implants as the treatment regime, as well as prognosis, depends on their presence. Nonetheless, ovarian IMT with GP has a better prognosis when compared with respective grades of primary IMT. In our review of 77 cases, though 45/77 cases were high grade IMT, 68/70 patients for whom data was available were alive. In 14.2% of our review cases, recurrence was reported. None of our 11 cases have reported recurrence so far.

Since GP is difficult to remove completely, residual disease is left post surgery in most of the cases. On rare occasions milliary spread of IMT has been reported. Post-surgery, chemotherapy induces a change in immature elements to mature elements. This is known as chemotherapeutic retroconversion or GTS (29). GP may sometimes be confused with GTS, especially when GP is diagnosed on second surgery. However, unlike GTS, it is not essential for GP to have a prior history of chemotherapy. Moreover, the implants associated with GP are composed exclusively of mature glial tissue, while GTS may have other mature teratoma components as well. This distinction between GP and GTS is critical to decide the further course of treatment. It is imperative in GTS cases to do an optimal cytoreductive surgery to avoid future complications, like bowel obstruction. Conversely, as GP cases are usually asymptomatic and known to be quiescent for long periods, they are managed by observation and follow up after the treatment of the primary associated OT (6). It is also believed that since nodal GP has a better prognosis, adjuvant chemotherapy is not recommended in such cases. Over a period, these GP foci either undergo fibroblastic transformation and gradually disappear or sometimes are detected at the time of second surgery (25,30). There is also a very rare chance for malignant transformation in GP. Shefren et al. (31) reported a 16-year girl with IMT with GP who developed a malignant glial neoplasm five years after the original surgery. Moreover, since GP with IMT cases are also associated with more frequent recurrences, a close, long-term follow-up is advised, given the rare but present chance for malignant transformation (31).

Study limitations

Although the incidence of GP is rare, 11 cases of GP are presented, along with IHC markers that suggest a stem cell origin of GP. Since only 11 cases were included, the absence of molecular confirmation following IHC immunopositivity of GP cells, confirming a stem cell origin, constituted the main limitation. More studies should be planned in future to establish a clear pathogenesis in these cases.

Conclusion

Though mostly associated with IMT, the incidence of MCT with GP was not infrequent. A possibility of GP must also be considered as a differential, clinically and radiologically, in cases of omental nodularity. Adequate sampling at the time of surgery is essential to rule out metastasis or GTS. The identification of mature glial tissue in primary ovarian neoplasm (with or without capsular breach/metastasis) associated with GP and nodal gliomatosis only favors the metaplastic theory of the origin of GP. SOX2, a stem cell marker inducing neural differentiation, may play a crucial role in the development of GP in association with other transcription factors. Since the prognosis is favourable and residual disease is dormant, a

conservative approach should be preferred, along with long-term follow-up to detect malignant transformation, if any. Further research must be taken to understand the factors contributing to the occurrence of GP and also for nodal gliomatosis.

Ethics Committee Approval: *Since this study was performed on retained histopathological samples from the departmental archives, ethics approval was not taken as per our institutional review board guidelines.*

Informed Consent: *Retrospective study.*

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