

Aggressive Gliomatosis Peritonei Arising from Ovarian Mature Teratoma with NF1 Mutation: A Case Report and Literature Review

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Background: GP arising from ovarian mature teratoma is a rare disease, and no confirmed pathogenesis signature genes are reported. The progress of GP is seen as relatively slow. Rare aggressive GP cases with poor prognosis were reported and no guidelines to follow for treatment.

Case Presentation: Herein, we report a 17-year-old girl with a 3-year-history of GP arising from ovarian mature teratoma. Surgeries and drug therapy were used to treat the aggressively growing tumour. Genetic profiling revealed the pathogenic mutation with potential therapeutic approaches. We firstly reported the NF1 mutations in GP secondary to teratomas and may cause bad prognosis.

Conclusion: GP arising from ovarian mature teratoma is rare; we found NF1 mutation could be the trigger of GP. The study may provide new insights into a better understanding of this rare disease.

Keywords: ovarian mature teratoma, gliomatosis peritonei, genetic profile, NF1 mutation, MGMT promoter methylation, Trametinib

Background

GP (gliomatosis peritonei) was firstly reported by Neuhäuser et al in 1906 with the character of mature glial tissue implanted on the surface of the peritoneum.¹ GP is usually secondary, the highest frequency of which was observed in ovarian teratoma.² Genetically, no pathogenic hereditary factors in the tumorigenesis of GP were confirmed. Most GP cases were described with benign behaviour.¹ Recently we encountered a case of GP arising from ovarian with aggressive biological features, and genetic profiling of the patient suggested NF1 mutation was involved in the development and progression of GP.

Case Presentation

The patient presented as an outpatient in our hospital in January 2021, with a 3-year history of GP secondary to mature teratoma. Back to late 2016 at the local hospital, under laparoscopy, a 10 cm roughly in diameter tumour was removed from the left ovary. Pathological examination revealed the cyst was a mature teratoma, with a large amount of nerve tissue. Seven months later the disease was found to recur. PET-CT revealed mass of the right ovary with metastasis to mesentery. Later, part of omentectomy with abdominal wall tumour resection was performed in the local hospital. Pathological examination showed peritoneal implantation of mature glioma derived from teratoma. Despite undergoing two operations, the glioma implantation lesions could not be completely removed, and MRI still showed multiple implanted metastatic nodules in the peritoneum after surgery. So, experimental chemotherapy in BEP regimen (D1~D5 cisplatin 20 mg iv + D1~D5 etoposide 100 mg iv + D1~D3 bleomycin 15 mg iv) was performed in the local hospital.

In September 2017, the patient first presented to the outpatient clinic in our hospital. PET-CT at our hospital showed recrudescence: right ovarian cyst; widely spread tumour with a large amount of fluid. We carried out left adnexa resection,

tumour cell reduction, right ovary biopsy, omentum resection, and appendectomy. During the surgery, we saw about 4000 mL yellow–brown ascites in the abdominal cavity; a huge pelvic–abdominal cavity mass extended from the back wall of the bladder to the lower part of the anterior abdominal wall, covering the intestinal tube, adhering to the bilateral appendage area and lateral pelvic wall, the texture of which was crumbly and like a sticky freeze, with the size of 25×20 cm; nodules on the surface of the small intestine, colon, and mesentery; while no obvious metastatic nodules were seen on the surface of the liver and spleen, spleen and diaphragm (Figure 1A and B). Pathological examination: left and right ovary: mature cystic teratoma of the ovary with a large amount of mature glial tissue; left fallopian tube, omentum, appendix, left pelvic wall nodules: glioma disease.

The patient was not followed up regularly after the surgery for personal reasons. In January 2021, the patient was admitted in our hospital after vomiting for two weeks as obvious symptoms due to intestinal obstruction. Radiographic examination suggested mass on the right adnexa area multiple nodules in the abdominal cavity, mesenteric and omentum. Laparotomy was performed. In the surgery, we saw ascites 8500 mL; the upper abdomen is sealed by adhesions, and the root contracture of the mesentery is chrysanthemum-shaped; the right adnexa was densely adhered to the sigmoid colon without a clear boundary (Figure 1C). Because the obstruction could not be relieved by surgery, a pelvic biopsy was finally performed. Pathological examination demonstrated the pelvic biopsy nodules were disseminated nodules of glioma. After the surgery, whole exome sequencing (WES), together with nervous system tumour molecular detection using the excised tumour sample and blood sample were applied. The genetic profiling suggested several pathogenic-related mutations (other results of point mutation, deletion, and insertion genes are displayed in the [Supplementary Table S1](#)):

Pathogenic germline mutation:

- NF1 gene splice site mutation c. 2850+2T>C (Table 1);

Pathogenic somatic mutation (Tables 2 and 3):

- MYC gene amplification (7.9 times);
- methylation on the promoter of MGMT gene (Figure 2);
- TERT gene C228T mutation;
- no meaningful mutation of IDH1 and 2 gene.

Combined with the gene analysis report, first-line chemotherapy drugs for glioma, Temozolomide, were used (Temozolomide 200 mg op QD, D1~D5, Q28D). The patient had no discomfort after the first three chemotherapy courses. However, after fourth course of treatment in June 2021, the patient developed discomfort such as nausea, abdominal pain, abdominal distension, and dyspnoea, following aggravating with vomiting. The imaging examination showed that the tumour had spread and metastasized widely with massive ascites. Abdominal drainage was performed, and Bevacizumab was used

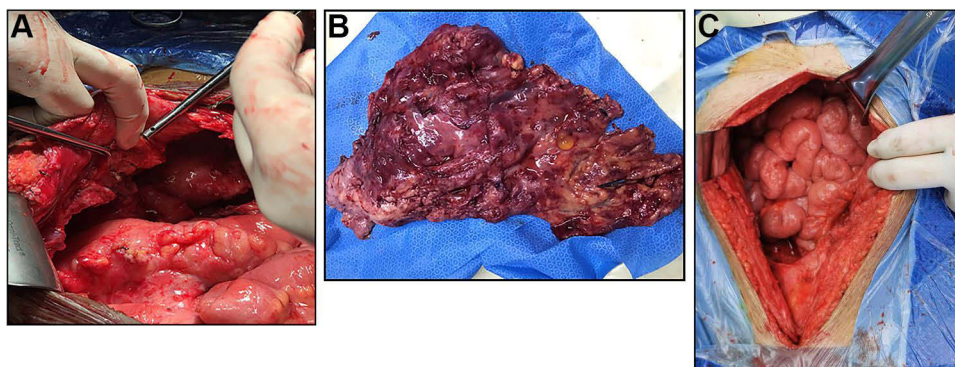


Figure 1 (A and B) Pictures from the surgery in 2017. (A) Part of the field of vision during the operation; (B) the resection specimen of part of the greater omentum. (C) Pictures from the surgery in 2021, the root of the mesentery shrunk into a chrysanthemum shape.

Table 1 Germline Variation Found in the Patient: NFI Gene Mutation

Gene Name	NFI
Mutation type	Splice site mutation
Nucleotide changes	c. 2850+2T>C
Amino acid changes	N/A
Frequency (%)	48.2
Chromosome	17
Exon	21/58
Transcript number	NM_0010 42492.2
Homozygous/heterozygous	Heterozygous
Risk of disease	Likely pathogenic

Table 2 Overview of the Whole Exome Sequencing and Solid Tumour Related Genes – Somatic Mutation

Items	Content	Results
Somatic gene mutation detection	Analysis of point mutations, deletions, and insertions on 21,000 genes	21 gene mutations
	Rearrangement analysis of 44 genes	No gene rearrangements
	Copy number analysis of 88 genes	MYC gene amplification (7.9 times)
Tumour mutational burden (TMB)	Analysis of point mutations, deletions, and insertions of 21,000 genes	0.69 muts/Mb
Microsatellite instability (MSI)	309 microsatellite sites (MS)	Microsatellite stable (MSS)
Chemotherapy single nucleotide polymorphism (SNP) site detection	45 SNP sites	No significant results
Tumour genetic susceptibility gene detection	148 tumour genetic susceptibility genes	Pathogenic germline mutations of the NFI gene

Table 3 Somatic Genetic Test Report of Brain Tumour Related Items

Items	Results
Methylation of MGMT promoter	Methylation
Loss of heterozygosity on chromosome 1p	Complete
Loss of heterozygosity on chromosome 19q	Complete
IDH1 gene R132 mutation	No mutation
IDH1 gene R172 mutation	No mutation
TERT gene C228T mutation	Mutation
TERT gene C250T mutation	No mutation
BRAF gene V600E mutation	No mutation

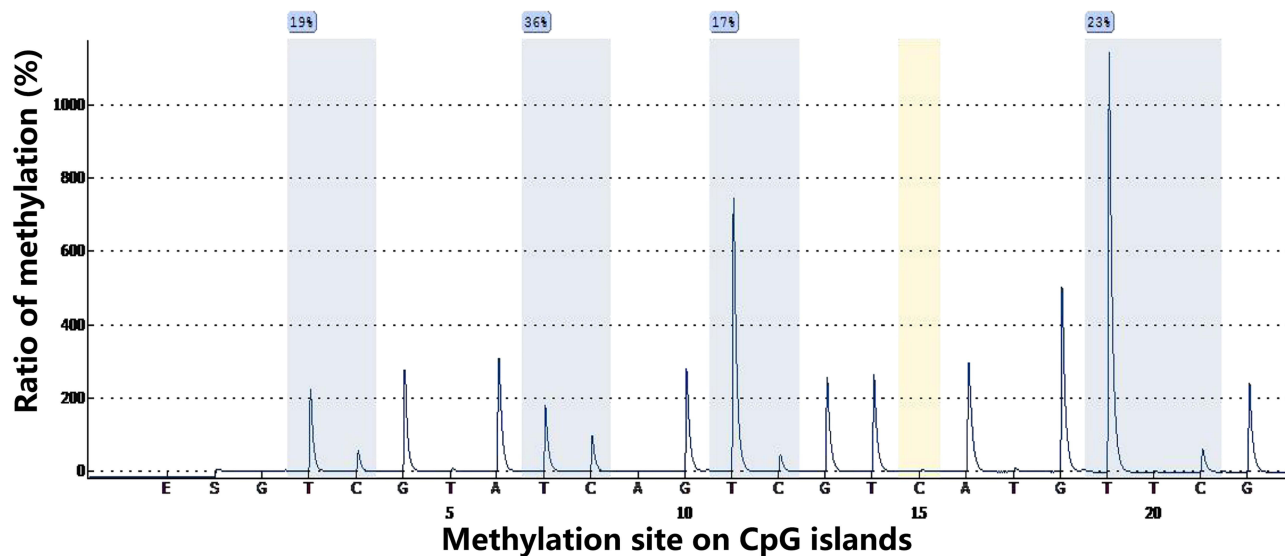


Figure 2 Detection of methylation of MGMT gene promoter CpG island using pyrosequencing.

(Bevacizumab 300 mL iv Q21D), followed by Temozolomide intensive therapy (Temozolomide 200 mg op QD, D1~D7, Q2W). After using Bevacizumab for the first time, the patient's symptoms, such as abdominal distension and vomiting, were improved. Nevertheless, after using Trametinib and bevacizumab cyclically for 2 courses, the patient increased ascites, abdominal distension, vomiting with difficulty breathing, and increased heart rate to 140 bpm. On 02–07–2021, we used Trametinib targeting for BRAF targeted therapy (Trametinib 2 mg, QD), with Endostatin to relieve ascites. However, the effect of targeted therapy is not obvious unfortunately, the patient's ascites progressed with a heart rate of up to 160 bpm. Finally, the patient died in August 2021 due to tumour-induced multiple organ failure.

Discussion and Conclusions

General Description

GP is a rare disease featured as metastatic implantation of mature glial tissue on the surface of the peritoneum, omentum, and abdominal lymph nodes,¹ firstly reported by Neuhäuser et al in 1906.³ GP is usually secondary to other diseases, most of the cases are associated with ovarian teratomas in any grade, and a few rare cases of GP come from gastric and gallbladder teratomas;² only individual cases suggest that GP is related to pregnancy and hydrocephalus ventricular-abdominal shunt.⁴ Most of the glial nodules are located on the surface of the peritoneum and pelvic organs, and a small number of cases are located on the surface of the liver, and even metastasize to the pleura.⁴ Common symptoms of GP include glioma lesions located in the peritoneum, accompanied by abdominal distension and ascites, and a small number of patients have lymph node metastasis and abdominal pain due to tumour torsion.¹ The diagnosis of GP is not difficult: GP could usually be pathologically diagnosed by HE-staining on tissue sections; and the neural marker, GFAP, could help to distinguish GP from low-grade epithelial ovarian tumours.⁵

Aetiology and Pathogenesis

At present, there are only about 100 cases of GP reported, so the cause of GP is not completely clear.⁶ Most cases of teratoma complicated by GP are considered to be caused by the rupture of the teratoma capsule leading to peritoneal metastatic carcinoma, and Robboy and Scully reported that 11 out of 12 cases are related to teratoma rupture or peritoneal adhesions.⁷ Ferguson et al conducted polymorphic microsatellite (MS) location analysis and demonstrated that the glial component in GP has nothing to do with ovarian teratoma, but comes from normal cells⁸, such as a certain pluripotent stem cell, which undergoes glial-directed differentiation under the stimulation of some factors secreted by the teratoma.⁹ The mechanism of GP may also include that after ventricular-peritoneal shunt, glial tissue is transferred

through the shunt and implanted into the peritoneum.¹⁰ In the case we reported, we suspected that the tumour ruptured before or during the first operation in the referring hospital, resulting in the spread of glioma components in the abdominal cavity and metastasis. However, the second pathogenesis mechanism mentioned above cannot be completely ruled out. In another word, patients who have not undergone ventricular-abdominal shunt, unless there is clear evidence of teratoma rupture, direct metastasis, or induced carcinogenesis, cannot be distinguished clearly. Different aetiology is accompanied with a different treatment scheme and prognosis.

General Treatment and Prognosis

Surgery is the first choice for treatment. As discussed before, GP always associated to ovarian teratoma in young patients. Therefore, for young female patients who have fertility requirements, regardless of the stage, the resection of the adnexa and omentectomy are recommended, plus suspicious lymph node biopsy,¹ and there is no need to perform pelvic lymph node dissection.¹ Because of the extensive planting of peritoneal glial nodules, it is usually very difficult to completely remove the diseased tissue to achieve R0. Thus, a postoperative BEP regimen chemotherapy was recommended.¹ In our case, when the patient came to our hospital, we performed left adnexa resection, tumour cell reduction, decomposition of complex intestinal adhesions, right ovary biopsy, omentum resection, and appendectomy. Although the biopsy of the right ovary revealed glioma implantation, considering the patient was young with the peritoneum extensively implantation, and it was impossible to remove all the lesions completely, we finally discussed that the patient's right ovary was preserved and only the primary left adnexa was removed.

Müller et al concluded three progressions of GP:⁶

1. GP was asymptomatic and detected by a secondary surgery;
2. GP may undergo "fibroblastic transformation" and gradually disappear;¹¹
3. GP may transform into malignant glial neoplasms such as glioblastoma which can result in patient death.¹²

In rare cases, a very small part of the patients had bad results due to the malignant transformation of the residual lesions.¹ Therefore, long-term postoperative follow-up is affirmative. Some researchers believe that follow-up can be conducted by referring to the follow-up principle for non-epithelial ovarian cancer.

The stage and grade of the primary teratoma and the grade of its metastatic tumours are related to the prognosis of teratoma.⁶ At present, most people believe that the biological behaviour of GP is benign, and GP usually has a favourable prognosis. Yoon et al reported that immature ovarian teratomas patients with GP presented more frequent recurrence and shorter recurrence-free survival, but the overall survival did not differ between immature ovarian teratomas with GP or without GP, due to most of the residual glial nodules of the peritoneum can be in a static state for a long time.¹³ Robboy and Scully demonstrated that the prognosis of GP is relatively good when it is composed of fully mature glial tissue.⁷ Liang et al suggested that immature ovarian teratomas with GP showed a better prognosis than primary immature teratomas of the same grade.⁹ Wang et al indicate that the presence of mature glial implants does not affect adversely the prognosis of ovarian teratoma.¹

Even though almost all the series of cases reported the GP patients had a good prognosis, our patient came out with a rather poor prognosis. The primary teratoma was defined as mature teratoma pathologically, it seemed the GP itself in the reported patient was rather aggressive, which may be induced by the heredity of the patient. Besides the patient we reported did not undergo regular follow-ups after surgery, which may be an important reason for the poor prognosis. The genetic analysis of the patient provided indication about treatment and prognosis. We only found TERT C228T mutation without mutation in IDH1 nor IDH2 gene, which might contribute to poor prognosis as previous research has shown in primary glioblastoma. Mutations in either genes of IDH1 or IDH2 suggest low risk, and TERT mutation alone instead of co-existing with IDH mutation suggests a poor prognosis.^{14,15} Although the star oncogene MYC amplification was found in the patient, limited treatment could be chosen for targeted therapy in GP.¹⁶ Patients with MGMT promoter methylation tend to benefit from Temozolomide treatment.^{17,18} MGMT promoter methylation was confirmed in the patient using pyrosequencing (Figure 2), so, we underwent Temozolomide on the patient and in the first four cycles of chemotherapy, the patient's symptoms were indeed relieved.

Genetic Analysis of NF1 in GP

At present, GP had no valuable susceptibility genes. However, the patient we reported carried genetic mutations related to the disease. NF1 gene splice site mutation c. 2850+2 T>C was found in WES. NF1 gene locates in 17q11.2,^{19,20} encoding the neurofibromin protein which belongs to GTPase activating protein (GAP) and plays the role as a tumour suppressor.²¹ Neurofibromatosis, an autosomal dominant genetic disease, is caused by germline mutations in NF1 and downstream deactivation of neurofibromin. The exact mutation we found in the patient, NF1 c. 2850+2 T>C, was not reported before, nor included as disease causing mutation in ClinVar and VarCards database. But a similar mutation at the same site, NF1 c. 2850+2 T>G (rs1597715880), was regarded as a likely pathogenic mutation for neurofibromatosis included in ClinVar database.^{22,23} We found these two single nucleotide variants did not affect the sequence of amino acid but may impact the structure and function of the protein.²² Meanwhile, the patient herself has the typical clinical feature of neurofibromatosis, café-au-lait macules (Figure 3), which was also found in her father and grandfather. In this manner, we believe that although the genetic mutation found in this patient has not been reported, analysing in gene and clinical level suggested the mutation may affect the protein structure, thereby affecting the function of neurofibromin losing the function as tumour suppressor. Neurofibromatosis is the most NF1 mutation related, but given the pathogenic mechanism of NF1 mutation, various tumours have been found to be related to NF1 mutation, including optic glioma, and high-grade glioma.^{22,23}

Neurofibromin contains a 300-residue domain similar to the Ras-GTPase activating protein family.²¹ Just like all the members in Ras-GAP family, neurofibromin could catalyse Ras protein from an active form (GTP-bound Ras) to an inactive form (GDP-bound Ras), and act as the negative regulators of the RAS proto-oncogene.^{21,24} In conclusion, loss of neurofibromin caused by NF1 mutation leads to constant activation of Ras, which then down streaming active the AKT–mTOR and MEK–ERK signalling pathways.^{21,24}

In our reported case, we believe that the NF1 germline mutation is related to the development and poor prognosis of GP. Since no NF1 mutation related GP cases were reported before, we can only explore treatment based on current experience. Considering the pathologic mechanism of NF1 germline mutation with silencing neurofibromin, we finally used Trametinib targeting MEK protein for experimental treatment. Unfortunately, the treatment effect is poor. NF1 is involved in the

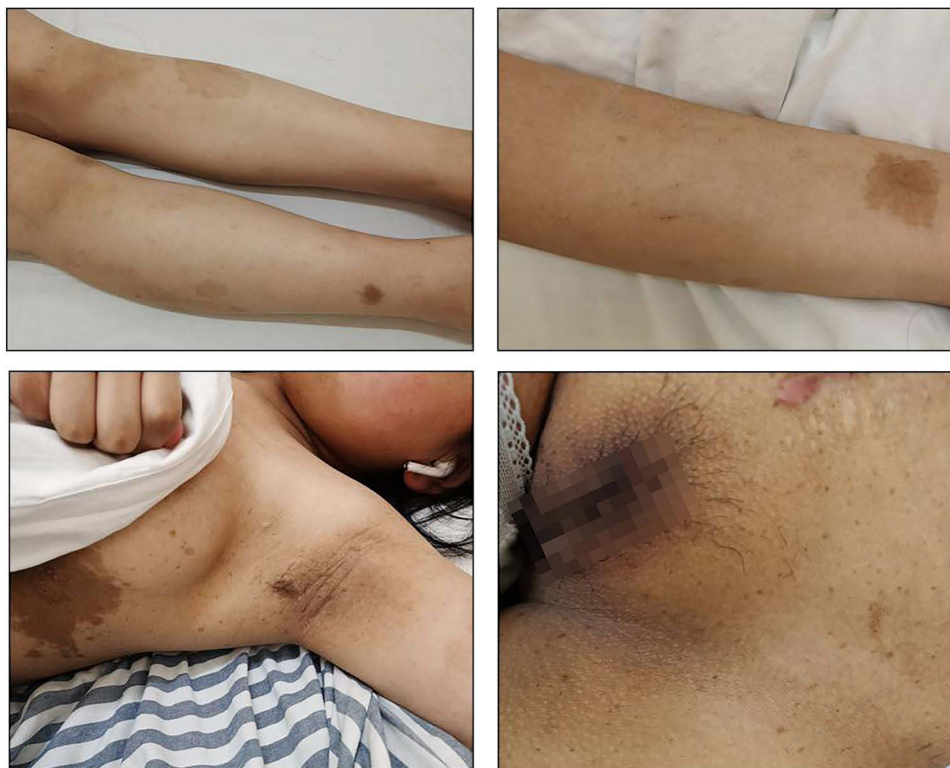


Figure 3 The café-au-lait macules on the skin surface of different parts of the patient's body.

regulation of Ras, which in turn regulates various downstream signalling pathways. It is possible that the activation of the MEK pathway has a low proportion in the development of GP, or the activation of other compensatory pathways results in insignificance of therapeutic of MEK inhibitors. The NF1 mutation may cause the GP, which should have been slow to progress, to be in a highly active state, and it is also an important reason for the poor prognosis of this case.

Conclusion

GP is a rare disease, and there was no susceptibility gene reported. We reported this patient with rather aggressive GP, which indicates NF1 mutation could be the reason triggering the GP, and NF1 should be considered as the potential oncogene inducing GP after ovarian teratoma.

Abbreviations

GP, gliomatosis peritonei; BEP, bleomycin, etoposide, and cisplatin; WES, whole exome sequencing; NF1, neurofibromatosis type 1; MYC, MYC proto-oncogene; MGMT, *O*-6-methylguanine-DNA methyltransferase; TERT, telomerase reverse transcriptase; IDH, isocitrate dehydrogenase; BRAF, B-Raf proto-oncogene; HE, haematoxylin and eosin; GFAP, glial fibrillary acidic protein.

Data Sharing Statement

The dataset used during the present study is available from the corresponding author (Weihua Lou, email: louweihua@renji.com) upon a reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent to participate was obtained from the patient's family.

Consent for Publication

Written informed consent has been obtained from the patient's family for publication of this paper and accompanying images.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicting interests in this work.

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