Title

Co-Localization of Gastrointestinal Stromal Tumors (GIST) and Peritoneal Mesothelioma: A Case Series

Journal

Annals of Surgical Oncology, 29(12)

ISSN

1068-9265

Authors

Courelli, Asimina S

Sharma, Ashwyn K

Madlensky, Lisa

et al.

Publication Date

2022-11-01

DOI

10.1245/s10434-022-12211-x

Peer reviewed

Published in final edited form as:

Ann Surg Oncol. 2022 November ; 29(12): 7542–7548. doi:10.1245/s10434-022-12211-x.

Co-Localization of Gastrointestinal Stromal Tumors (GIST) and Peritoneal Mesothelioma: A Case Series

Asimina S. Courelli, MD[1], **Ashwyn K. Sharma, MD**[1,2,3], **Lisa Madlensky, PhD**[2,3,4], **Yoon Young Choi, PhD**[1,2], **Sam Li, PhD**[1,2], **Shirley Sarno**[1,2], **Kaitlyn Kelly, MD**[1,2,3], **Winta Mehtsun, MD, MPH**[1,2,3], **Santiago Horgan, MD**[3,5], **Olivier Harismendy, PhD**[2,3,6], **Joel M. Baumgartner, MD**[1,2,3], **Jason K. Sicklick, MD**[1,2,3]

[1]Division of Surgical Oncology, Department of Surgery, University of California, San Diego, CA

[2]Moores Cancer Center, La Jolla, CA

[3]School of Medicine, University of California, San Diego, CA

[4]Division of Medical Genetics, Department of Medicine, University of California, San Diego, CA

[5]Division of Minimally Invasive Surgery, Department of Surgery, University of California, San Diego, CA

[6]Division of Biomedical Informatics, Department of Medicine, University of California, San Diego, CA

Abstract

Purpose.—Gastrointestinal stromal tumor (GIST) is associated with increased risk of additional cancers. In this study, synchronous GIST, and peritoneal mesothelioma (PM) were characterized to evaluate the relationship between these two cancers.

Methods.—A retrospective chart review was conducted for patients diagnosed with both GIST and PM between July 2010 and June 2021. Patient demographics, past tumor history, intraoperative reports, cross-sectional imaging, peritoneal cancer index (PCI) scoring, somatic next-generation sequencing (NGS) analysis, and histology were reviewed.

Results.—Of 137 patients who underwent primary GIST resection from July 2010 to June 2021, 8 (5.8%) were found to have synchronous PM, and 4 patients (50%) had additional cancers and/or benign tumors. Five (62.5%) were male, and the median age at GIST diagnosis was 57 years (range: 45–76). Seventy-five percent of GISTs originated from the stomach. Of the eight patients, one patient had synchronous malignant mesothelioma (MM), and the remaining had well-differentiated papillary mesothelioma (WDPM), which were primarily located in the region of the primary GIST (89%). The median PCI score was 2 in the WDPM patients. NGS of GIST

J. K. Sicklick, MD, jsicklick@health.ucsd.edu.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1245/s10434-022-12211-x.

DISCLOSURE J.K.S. receives research funds from Foundation Medicine Inc. and Amgen; consultant fees from Deciphera and Grand Rounds; speakers fees from Deciphera, La-Hoffman Roche, Foundation Medicine, Merck, and QED; owns stock in Personalis. A.S. received financial support through the NIH T32 CA121938 Cancer Therapeutics (CT2) Training Fellowship. All other authors have no competing interests.

revealed oncogenic KIT exon 11 (62.5%), PDGFRA D842V (25%), or SDH (12.5%) mutations, while NGS of the MM revealed BAP1 and PBRM1 alterations.

Conclusions.—One in 17 GIST patients undergoing resection in this series have PM, which is significantly higher than expected if these two diseases were considered as independent events. Our results indicate that synchronous co-occurrence of GIST and PM is an underrecognized finding, suggesting a possible relationship that deserves further investigation.

Gastrointestinal stromal tumors (GIST) constitute the most common mesenchymal tumor of the gastrointestinal tract. They arise from the Interstitial Cells of Cajal—intestinal peristaltic pacemaker cells—with an incidence of approximately 7 cases per million in the United States.[1,2] GIST most commonly develop in the stomach (55%) and most often are driven by mutations in *KIT* (65–80%) or *PDGFRA* (5–10%).[1,2] Although GIST are seen in isolation in a majority of cases, several single-institution studies have shown that 14–33% of GIST occur in patients with other malignancies, despite no known hereditary syndrome outside of Carney-Stratakis syndrome, associated with germline *SDHx* mutations, and neurofibromatosis type 1, associated with germline *NF1* mutations.[3–8] In 2015, our group analyzed the Surveillance, Epidemiology, and End Results (SEER) database and found that 17.1% of 6,112 GIST patients had additional cancers.[3] In that SEER analysis, mesothelioma was one of the cancers that exhibited increased co-occurrence both before (7.35-fold) and after (2.43-fold) GIST diagnosis.[3] However, GIST co-occurrence with peritoneal mesothelioma, a mesothelioma subtype found only in the abdominal cavity, remains poorly understood.

Peritoneal mesothelioma (PM) affects older adults—men and women equally—with 2 cases per million each year.[9] PM can be classified as borderline, which includes well-differentiated papillary mesothelioma (WDPM) subtypes, or malignant mesothelioma (MM), which includes epithelioid, biphasic, and sarcomatoid variants.[9,10] Recent studies have shown that mutations in deubiquitinase BRCA1-associated protein-1 (BAP1) are associated with the development of more than half of MM cases.[11]

At present, spatial and genomic links between GIST and PM remain unknown. In this case series, we examined disease presentation, diagnosis, treatment, and tumor genomic profiles of patients diagnosed with both GIST and PM to characterize the co-occurrence of these two rare intra-abdominal cancers, and to identify features which may suggest a unique pathological process for co-occurrence.

METHODS

Patient Demographics and Clinicopathological Features

A retrospective study of surgical patients diagnosed with GIST between July 2010 and June 2021 was conducted. Patients diagnosed with both GIST and PM during that period were selected for analysis following Institutional Review Board approval. Data on patient age, gender, race, past tumor history, and disease recurrence at most recent follow-up was collected. GIST was characterized by size, location, mitotic index, and histological subtype. PMs were characterized by histological subtype, location, and peritoneal cancer index (PCI) score (see below)—a measure of disease burden.[12]

PCI Scoring

The disease burden of each PM was quantified using the PCI score (0–39).[12] The abdominal cavity and small intestine are divided into 13 regions, each of which was inspected intraoperatively for the presence of PM.[12] If nodules were identified, their diameter was measured and recorded prior to nodule dissection. Based on maximum nodule/mass diameter (d^{max}) in each PCI abdominal region, a score of either 0 (d_{max} = 0 cm), 1 (d_{max} = 0.5 cm), 2 (d_{max} = 5 cm), or 3 (d_{max} > 5 cm or confluence) was assigned.[12] Only nodules histologically diagnosed as PM were used in the PCI calculation—inclusion cysts were excluded.

Tumor Genetic Analysis

Somatic genomic profiles for GIST and PM from resected tumors and germline genetic analyses of patient blood samples (when available) were obtained using commercially available CLIA (Clinical Laboratory Improvement Amendments)-approved next generation sequencing (NGS) assays from Tempus (tumor: 648 gene panel; blood: 105 gene panel), Foundation Medicine (324 gene panel), Invitae (84 gene panel), Guardant360 (83 gene panel), and Caris (570 gene panel). Mutations were classified in the CLIA NGS results as somatic or germline and pathogenic or variants of unknown significance (VUS). Sequencing for Patient 1 (GIST only), Patient 2 (GIST and blood), Patient 7 (GIST only), and Patient 8 (GIST only) was conducted using the Tempus panels (Fig. 1B). Sequencing for Patient 3 (GIST only), Patient 4 (GIST and PM) was conducted using the Foundation One panels (Fig. 1B). For Patient 5, GIST and PM sequencing was conducted using the Tempus panels and germline sequencing was conducted on whole blood using the Invitae panel (Fig. 1B). For Patient 6, GIST sequencing was conducted using the Caris Life Sciences tumor panel and germline sequencing was conducted using the Invitae panel (Fig. 1B). The sequencing depth and MAF for variants reported by each of these assays can be found in Supplemental Table 1.

RESULTS

Patient Demographics and Tumor History

During the 11 years from July 2010 to June 2021, 137 patients (46.9%) of 292 GIST patients evaluated at UC San Diego underwent GIST resection at our institution. Eight of these patients were diagnosed with synchronous GIST and PM. Five (62.5%) were male, and three were female. Consistent with our region’s demographics, six were Caucasian, one was Asian/Pacific Islander, and one was African American (Fig. 1A). The median age at GIST diagnosis was 57 years (range: 45–76; Fig. 1A). Seven of eight patients underwent resection of their primary GIST at UC San Diego. One patient underwent right hepatectomy and hepatic wedge resections for metastatic GIST 3 years after primary gastric GIST resection. Four of the eight patients had a history of other malignancies and/or benign tumors. Patient 2 had a history of non-Hodgkin’s lymphoma (NHL) and meningioma. Patient 4 had a history of renal cell carcinoma (RCC) and polycythemia vera (PV). Patient 5 had a history of prostate cancer (PrCa) and a gallbladder adenomyoma. Patient 7 had a history of ovarian serous cystadenoma (Fig. 1A).

Clinicopathological Features of GIST and PM

In all eight cases, GIST was diagnosed first, and PM was noted during either GIST resection or diagnostic evaluation. Intraoperative findings and pre-resection CT scans indicated that primary GISTs originated from the lesser curvature of the stomach in 50% of patients, the fundus in 12.5% of patient, the antrum in 25% patient, and the small bowel in 12.5% of patients (Fig. 1A; Table 1). The median size of GIST was 13.8 (range: 4.2–17.0) cm (Fig. 1A; Table 1). Histological analysis revealed that of the resected GIST, 37.5% had a spindle cell morphology, 25% had an epithelioid morphology, and 37.5% had a mixed spindle-epithelioid morphology (Fig. 1A). The median mitotic index was 3 mitoses per 5 mm^2 (range: 1–68) (Fig. 1A). R0 GIST resection was performed in all seven primary GIST resections. Patient 8 underwent multiple hepatic wedge resections for multifocal metastatic SDHB-deficient GIST.

Histopathological analysis of PM tissue obtained during peritoneal cytoreduction revealed two types of mesotheliomas: well-differentiated papillary mesothelioma (WDPM) in seven patients (87.5%), and malignant mesothelioma (MM) in one patient (12.5%) (Fig. 1A; Table 1). All 13 PCI regions were extensively visually and manually inspected for the presence of nodules or other abnormalities in each case except for patient 5, for whom the resection and cytoreduction was conducted laparoscopically and only 6 of 13 regions were explored. Except for patient 4, who had known malignant mesothelioma at the time of GIST resection, all other cytoreductions were conducted in the absence of a histologic diagnosis. A subset of these cytoreduced nodules were peritoneal inclusion cysts and were not included in the final PCI calculation. The size of all lesions is also described below. The median PCI score was 2 (range: 1–17), with WDPM patients having a median PCI score of 2 (range: 1–3) and the one MM patient having a PCI score of 17 (Fig. 2). Seven patients underwent complete (CC0) cytoreduction for PM in all 13 PCI regions, whereas patient 5 underwent laparoscopic cytoreduction, which allowed only 6 of 13 regions to be fully visualized. Patient 1 had one nodule measuring 0.3 cm; patient 2 had two nodules each measuring 0.1 cm; patient 3 had two nodules measuring 1.2 cm and 1.7 cm; patient 4 had diffuse nodules throughout the abdomen of variable size, ranging from 0.1 up to 4.5 cm; patient 5 had a single nodule measuring 1.5 cm; patient 6 had several nodules with 1.7 cm maximum diameter; patient 7 had three nodules along the posterior gastric wall measuring approximately 0.3 cm and a nodule near the ligament of Treitz measuring 0.8 cm; patient 8 had a 0.4 cm mesenteric lesion and three terminal ileum mesenteric nodules measuring up to 1.5 cm.

Co-occurrence of Tumors

Lesions were identified at the time of GIST resections and suspected to be small volume peritoneal GIST metastases at the time of resection. As noted, final pathology revealed PM in these cases. Based on operative note descriptions of the tumor locations, six of seven (86%) WDPM patients were noted to have mesothelioma nodules near the GIST, and all were characterized as having disease in the PCI region of the primary GIST (Fig. 2). Patient 8 did not display the same co-localization of GIST and WDPM, because the metastatic GIST was confined to the liver and the WDPM to the terminal ileum mesentery. Although Patient 4 had extensive MM distributed throughout much of his peritoneal cavity, the disease burden was most concentrated in the left upper quadrant, which included the gastric surface (Fig. 2).

GIST and PM Genomics

Following GIST resection and PM cytoreduction, tumor samples were obtained for commercial NGS to identify potentially oncogenic mutations present in the GIST and the PM to guide clinical management. Of the eight patients, five GIST had a *KIT* exon 11 mutation (62.5%), two had *PDGFRA* D842V mutations (25%), and one had a *SDHA* mutation (12.5%) (Fig. 1B; Table 1). Aside from these canonical GIST driver mutations, seven additional mutations were classified as pathogenic on GIST NGS (Patient 2: STAG2, Patient 3: PTCH1 and YY1A1P, Patient 6: ATM, DNMTA3, and RB1, Patient 7: RBM10 and KMT2D; Patient 8: TP53). NGS of the MM revealed BAP1 and PBRM1 alterations. Seventeen additional variants identified on somatic GIST and PM NGS, as well as germline sequencing were classified as variants of unknown significance (VUS) (Fig. 1B; Table 1).

Outcome and Patient Follow-up

Following resection and cytoreduction, the patients were followed for recurrence of GIST and/or PM. All eight patients were without GIST recurrence at a median followup of 14 months (range: 1–75). The seven patients diagnosed with WDPM remained without PM disease recurrence at a median follow-up of 12 months (range: 1–75), whereas the patient diagnosed with MM experienced recurrence at 5 months postoperatively despite complete cytoreduction and hyperthermic intraperitoneal chemotherapy.

DISCUSSION

In this study, we investigated the spatial co-occurrence, as well as tumor genomic patterns in GIST and PM as our group's prior publications on the relationship between GIST and PM were limited to population-based studies. Seven of eight patients in our series exhibited co-localization of GIST and PM. These patients were noted to have the highest PM disease burden near the primary GIST. Together, our findings raise several questions about the relationship between these malignancies.

GIST has an incidence of about 7 cases per million and PM has an incidence of 2 cases per million.[1,9] If GIST and PM co-occurred independently, their incidence would be in the order of 1.4×10^{-9}%. However, the conditional incidence of 6% of the occurrence of PM given the occurrence of GIST implies that the incidence of the synchronous co-occurrence of GIST and PM is on the order of 3.5×10^{-5}%. That is, the incidence of the synchronous GIST and PM co-occurrence is significantly higher than the incidence of independent co-occurrence with six orders of magnitude difference. Analogously results were reported by Sun et al. in a series of 75 WDPM cases, where GISTs were identified in 19.3% of WDPM cases during surgery.[13] In that series, the incidence of GIST identification during WDPM surgeries was significantly higher than the computed co-incidence of the independent GIST and PM in the general population (1.4 per trillion) and similar to the results reported in our current series (6%). Potential biases affecting the reporting of WDPM and possibly leading to an under-reporting of GIST and PM co-occurrence are lack of awareness and limited ability to evaluate patients for certain peritoneal-based cancers without operative exploration. A previous study, investigating second cancer diagnoses in GIST both before and after GIST diagnosis (Smith et al.), proposed surveillance bias

as a potential contributing factor for the increased incidence of second cancers in GIST patients, as they undergo frequent imaging for preoperative planning and postoperative surveillance.[14] However, surveillance bias is unlikely to affect incidence of PM, because this tumor type is typically not visualized on standard cross-sectional imaging modalities used for cancer screening. Clinically, identification of a second cancer has effects on post operative treatment as well as influences prognosis. Diagnosis of peritoneal disease as PM as opposed to metastatic GIST changes the need for post-operative chemotherapy. As reported in Smith et al., diagnosis of second cancers in GIST patients provides prognostic information. Patients with diagnosis of additional malignancies diagnosed within 6 months of GIST diagnosis had a poorer 5 year survival (54%) compared with patients who did not have any additional cancer diagnoses (65%).[14] The high co-occurrence rates of GIST and PM relative to the independent incidence of each one suggests the potential for a local, nonindependent, symbiotic relationship between GIST and PM that may lead to the synchronous co-localization of these cancers. Our findings indicate that patients undergoing surgery for GIST also should be evaluated for the presence of GIST metastases and other primary and/or metastatic peritoneal malignancies. Underdiagnosis of concurrent peritoneal disease or misattribution of disease to metastatic GIST both have important ramifications for adjuvant therapy. For example, if peritoneal disease is GIST associated WDPM as opposed to metastatic GIST, the patient may not require systemic therapy postoperatively.

One explanation for a more frequent finding of multiple primary tumors is an underlying hereditary cancer predisposition. Of the eight patients with both GIST and PM, four patients also had a history of multiple additional tumors, including non-Hodgkin’s lymphoma and meningioma, renal cell carcinoma and polycythemia vera, prostate cancer and gallbladder adenomyoma, or ovarian serous cystadenoma. However, in our series, no common pathogenic germline mutations were identified in patients who had germline testing, either as a germline test (patients 5 and 6) or those who had a paired blood sample analyzed along with tumor profiling (patient 2). To date, BAP1 is the only gene associated with a germline predisposition to mesothelioma. Patients 2 and 5 were found to have a germline VUS in BAP1; however, there is no evidence at the present time that either of these variants are potentially pathogenic. One of the VUS (R114H) is classified in ClinVar as ‘‘likely benign’’ or as a VUS by various labs (Variation ID 346125). A functional study of this variant did not demonstrate any change in deubiquitinase activity (PMID: 28062663). The other variant (c.375–5C>T; ClinVar Variation ID 539944) has two labs calling the variant as likely benign and one lab calling the variant as a VUS. Although no consensus exists for a characteristic gene mutation profile in WDPM, Stevers et al. reported have mutually exclusive mutations in TRAF7 and CDC42 with a relative absence of mutations in BAP1 while Shrestha et al. characterized a series of 5 incidentally found WDPMs and noted that COSMIC signature 24 (enriched for C > A transversion substitutions) was the dominant signature in their series. This variant is hypothesized to be related to aflatoxin exposure.[15–17] Our findings suggest that some other mechanism(s) may be involved in this specific signature since none of our patients are known to have aflatoxin exposure and previously reported mutations in TRAF7 or CDC42 were not identified in the one WDPM in our series that underwent NGS.

Co-localization of gastric GIST and PM tumors was noted in seven of eight patients, pointing towards a potential interdependency between the two tumors. Although the

stomach is the most common location for development of GIST, focal involvement of PM in the GIST-localized region of the peritoneal membrane deviates from canonical PM, which typically uniformly involves the entire peritoneal membrane.[9] Interestingly, focal involvement of PM in close proximity to other cancers has been previously described.[18] For instance, WDPM has been reported to co-occur with gastric, hepatocellular, and colorectal carcinomas, as well as has been found in close proximity to uterine adenomatoid and ovarian tumors.[19–22] Co-localization was not observed in the case of only one patient in our series. However, the patient had already undergone resection of the primary GIST and was being surgically treated for hepatic-only metastases. Deviation from the typical diffuse disease distribution of PM suggests a focal process for GIST and PM colocalization that potentially involves the first tumor facilitating the initiation or progression of the second tumor. Transfer of oncogenic mediators by GIST-originating exosomes is an intriguing possible mechanism. GIST have been shown to release exosomes containing oncogenic KIT and proteins involved in VEGF, MAPK, and Wnt signaling, which can induce genetic changes in surrounding cells.[23–25] It remains to be determined if the effect of GIST on the development of PM, or vice versa, also may be correlated with the extent of the first tumor, and whether the co-localization of GIST and PM tumors has ramifications for different patterns of local recurrence. Furthermore, colocalization of GIST with other peritoneal malignancies, whether primary or metastatic, remains to be investigated. Of the seven patients with WDPM without PM, no evidence of disease recurrence was observed at 12 months, which leads us to inquire whether the local tumor micro-environment is unique amongst these PM tumors co-localizing with GISTs. Longer follow-up will help to further understand whether unique recurrence patterns exist for these tumors.

The main limitations to this study are the small patient population and constraints in identification of GIST patients with PM. Even though our calculations demonstrate that a potentially nonrandom relationship between the likelihood of PM development in GIST, both GIST and PM are relatively rare intra-abdominal cancers. Therefore, even in a high-volume GIST center and a high-volume PM center, few patients would be diagnosed with both GIST and PM. Second, we were only able to evaluate the presence of PM in patients who underwent surgery for GIST. Unless a patient has significant disease burden, which may be mistaken for GIST, it is not possible to diagnose PM exclusively from imaging. Therefore, the primary patient population in our study evaluated for the presence of both GIST and PM includes patients undergoing surgery for GIST, during which the abdomen could be thoroughly evaluated for further disease. In our GIST database, 53.1% of GIST patients were not evaluated for peritoneal malignancy, because they did not undergo surgery for GIST at our center and were not previously known to have PM. Finally, not all patients were amenable to germline testing and therefore we could not undertake a more in-depth analysis of possible germline mutations that may predispose patients to both types of tumors.

CONCLUSIONS

The differences in synchronous GIST and PM disease presentation compared with GIST or PM in isolation, as well as the co-localization of both tumors suggest a non-independent

relationship between synchronous GIST and PM. This relationship may be associated with tumor symbiosis and/or unappreciated genomic drivers that warrant further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES

1. Ma GL, Murphy JD, Martinez ME, et al. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer Epidemiol Biomark Prev 2015;24:298–302.
2. Patil DT, Rubin BP. Gastrointestinal stromal tumor: advances in diagnosis and management. Arch Pathol Lab Med 2011;135:1298–310. [PubMed: 21970485]
3. Murphy JD, Ma GL, Baumgartner JM, et al. Increased risk of additional cancers among patients with gastrointestinal stromal tumors: a population-based study. Cancer 2015;121:2960–7. [PubMed: 25930983]
4. Ferreira SS, Werutsky G, Toneto MG, et al. Synchronous gastrointestinal stromal tumors (GIST) and other primary cancers: case series of a single institution experience. Int J Surg 2010;8:314–7. [PubMed: 20380900]
5. Ponti G, Luppi G, Martorana D, et al. Gastrointestinal stromal tumor and other primary metachronous or synchronous neoplasms as a suspicion criterion for syndromic setting. Oncol Rep 2010;23:437–44. [PubMed: 20043105]
6. Chen CI, Castellanos MB, Ruch MA, et al. Gastrointestinal stromal tumor with synchronous colorectal adenocarcinoma. QJM 2017;110:591–2. [PubMed: 28655207]
7. Comandini D, Damiani A, Pastorino A. Synchronous GISTs associated with multiple sporadic tumors: a case report. Drugs Context 2017;6:212307. [PubMed: 29167690]
8. Pandurengan RK, Dumont AG, Araujo DM, et al. Survival of patients with multiple primary malignancies: a study of 783 patients with gastrointestinal stromal tumor. Ann Oncol 2010;21:2107–11. [PubMed: 20348145]
9. Greenbaum A, Alexander HR. Peritoneal mesothelioma. Transl Lung Cancer Res 2020;9:S120–32. [PubMed: 32206577]
10. Sugarbaker PH, Welch LS, Mohamed F, et al. A review of peritoneal mesothelioma at the Washington cancer institute. Surg Oncol Clin N Am 2003;12(605–21):xi.
11. Cheung M, Testa JR. BAP1, a tumor suppressor gene driving malignant mesothelioma. Transl Lung Cancer Res 2017;6:270–8. [PubMed: 28713672]
12. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res 1996;82:359–74. [PubMed: 8849962]
13. Sun M, Zhao L, Yu L, et al. Well differentiated papillary mesothelioma: a 17 year single institution experience with a series of 75 cases. Ann Diagn Pathol 2019;38:43–50. [PubMed: 30419426]
14. Smith MJ, Smith HG, Mahar A, et al. The impact of additional malignancies in patients diagnosed with gastrointestinal stromal tumors. Int J Cancer 2016;139(8):1744–51. [PubMed: 27299364]
15. Stevers M, Rabban JT, Garg K, et al. Well-differentiated papillary mesothelioma of the peritoneum is genetically defined by mutually exclusive mutations in TRAF7 and CDC42. Mod Pathol 2019;32:88–99. [PubMed: 30171198]
16. Shrestha R, Nabavi N, Volik S, et al. Well-differentiated papillary mesothelioma of the peritoneum is genetically distinct from malignant mesothelioma. Cancers (Basel) 2020;12:1568. [PubMed: 32545767]
17. Yu W, Chan-On W, Teo M, et al. First somatic mutation of E2F1 in a critical DNA binding residue discovered in well-differentiated papillary mesothelioma of the peritoneum. Genome Biol 2011;12:R96. [PubMed: 21955916]

18. de la Torre J, Banerjee S, Baumgartner J, et al. Tumor symbiosis: gastrointestinal stromal tumor as a host for primary peritoneal mesothelioma. J Gastrointest Surg 2019;23:879–81. [PubMed: 30132292]

19. Kim M, Kim HS. Clinicopathological characteristics of well-differentiated papillary mesothelioma of the peritoneum: a single-institutional experience of 12 cases. In vivo 2019;33:633–42. [PubMed: 30804152]

20. Malpica A, Sant'Ambrogio S, Deavers MT, et al. Well-differentiated papillary mesothelioma of the female peritoneum: a clinicopathologic study of 26 cases. Am J Surg Pathol 2012;36:117–27. [PubMed: 22024662]

21. Rathi V, Hyde S, Newman M. Well-differentiated papillary mesothelioma in association with endometrial carcinoma: a case report. Acta Cytol 2010;54(5 Suppl):793–7. [PubMed: 21053542]

22. McGinnis JM, Bloomfield V, Kazerouni H, Helpman L. Well-differentiated papillary mesothelioma with two synchronous serous gynaecologic carcinomas in a 62-year-old woman: lessons learned for the gynaecologic surgeon. J Obstet Gynaecol Can 2020;42(10):1262–6. 10.1016/j.jogc.2019.12.012. [PubMed: 32173236]

23. Atay S, Banskota S, Crow J, et al. Oncogenic KIT-containing exosomes increase gastrointestinal stromal tumor cell invasion. Proc Natl Acad Sci 2014;111:711–6. [PubMed: 24379393]

24. Atay S, Godwin AK. Tumor-derived exosomes: a message delivery system for tumor progression. Commun Integr Biol 2014;7:e28231. [PubMed: 24778765]

25. Atay S, Wilkey DW, Milhem M, et al. Insights into the proteome of gastrointestinal stromal tumors-derived exosomes reveals new potential diagnostic biomarkers. Mol Cell Proteomics 2018;17:495–515. [PubMed: 29242380]

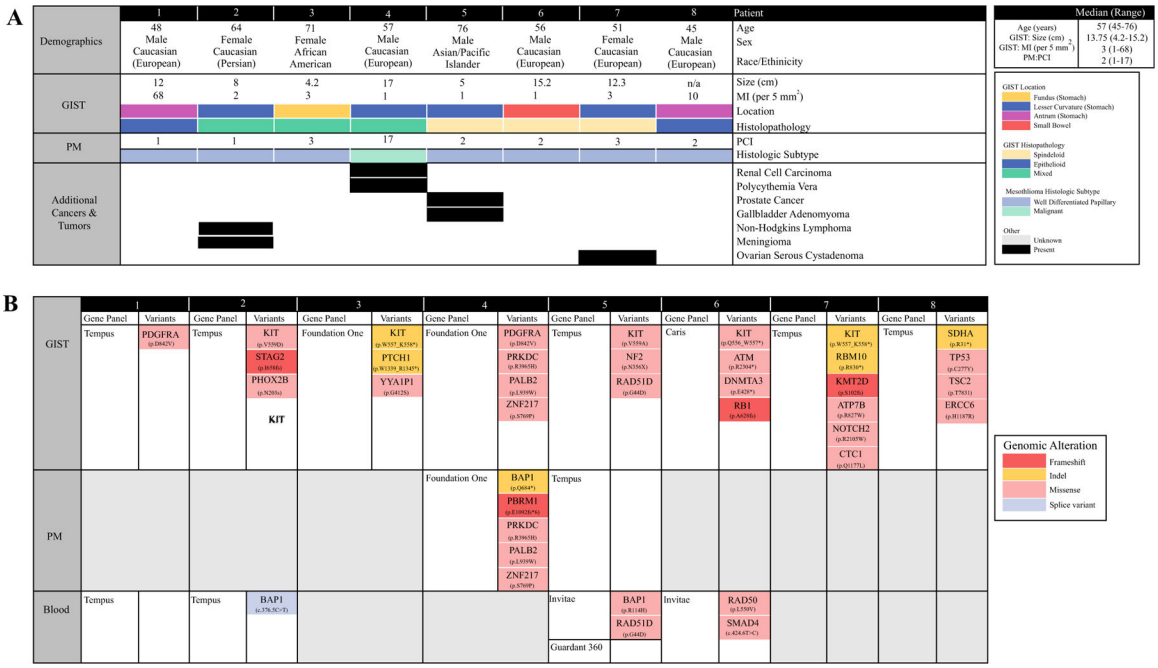

FIG. 1.

GIST and PM characterization. A Co-mutation plot of patient data, cancer history, GIST and PM clinicopathological features, tumor genomic analyses, and germline genetic analyses. Data for each patient is listed in columns by case number, and are color-coded according to the legend. B Tabulation of NGS tumor panel results for each tumor and/or germline analyzed. Columns represent data for each patient that are subdivided into columns for the specific NGS assay conducted. Rows represent the tissue used for each NGS panel

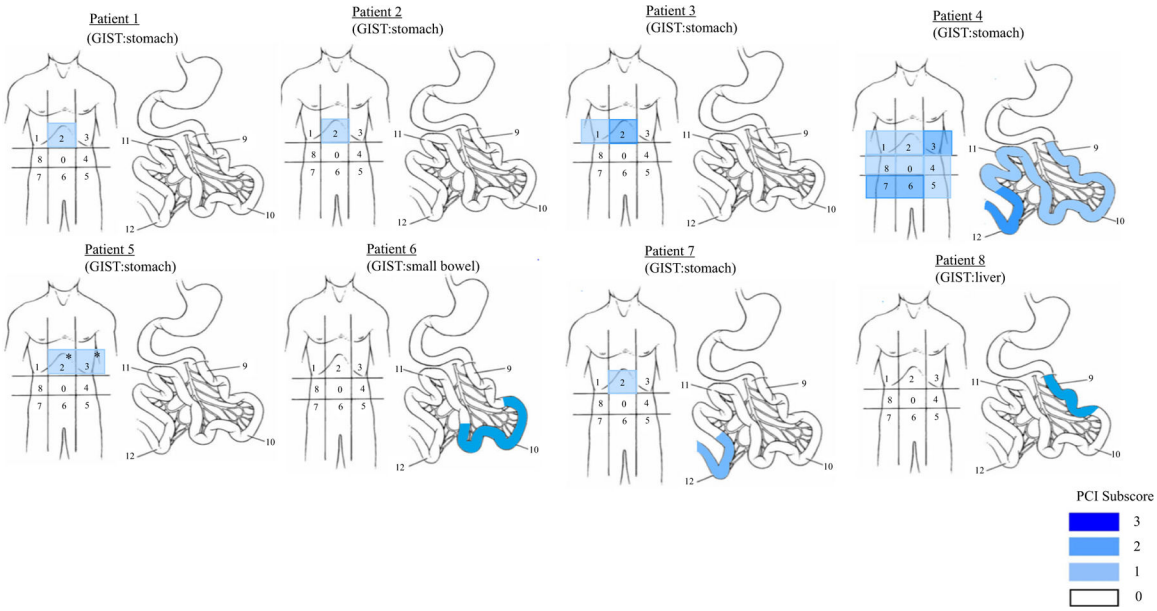

FIG. 2.

Anatomical map of Peritoneal Cancer Index (PCI) for each patient. PCI subscores (0, 1, 2, 3) in each abdominal/pelvic region are shown for each patient. Dark blue indicates a regional subscore of 3, medium blue indicates a regional subscore of 2, light blue indicates a regional subscore of 1, and white indicates a regional subscore of 0.

**Note* only 6 of the 13 PCI regions were explored in patient 5 due to laparoscopic cytoreduction

TABLE 1

Patient demographics and tumor clinicopathological features

Characteristic	Number (%)
Age at diagnosis (yr)	
Median [range]	57 [45–76]
Gender	
Male	5 (63%)
Female	3 (37%)
Race/ethnicity	
African American	1 (12.5%)
Asian/Pacific Islander	1 (12.5%)
Caucasian	6 (75%)
GIST	
Size (median [range], cm)	13.8 [4.2–15.2]
Mitotic index (median [range], per 5 mm^2)	3 [1–68]
GIST location (primary)	
Fundus	1 (12.5%)
Lesser curvature	4 (50%)
Antrum	2 (25%)
Small bowel	1 (12.5%)
GIST histopathology	
Spindeloid	3 (38%)
Epithelioid	2 (25%)
Mixed	3 (38%)
GIST driver mutation	
KIT (exon 11)	5 (63%)
PDGFRA D842V	2 (25%)
SDHA	1 (12.5%)
PM PCI	
Median [range]	2 [1–17]
PM subtype	
Well differentiated papillary mesothelioma	7 (87.5%)
Malignant mesothelioma	1 (12.5%)

GIST gastrointestinal stromal tumor, *PM* peritoneal mesothelioma, *PCI* peritoneal carcinomatosis index