OPEN ACCESS

Complete clinical remission of malignant peritoneal mesothelioma with systemic pemetrexed and bevacizumab in a patient with a BAP1 mutation

Jimmy Lee ,[1] Jordan Turetsky,[1] Elham Nasri,[2] Sherise C Rogers[3]

[1]University of Florida College of Medicine, Gainesville, Florida, USA
[2]Department of Pathology, Immunology and Laboratory Health, University of Florida Health, Gainesville, Florida, USA
[3]Department of Medicine, Division of Hematology & Oncology, University of Florida Health, Gainesville, Florida, USA

Correspondence to
Dr Sherise C Rogers;
sherise.rogers@medicine.ufl.edu

Accepted 2 November 2023

SUMMARY

Malignant peritoneal mesothelioma (MPeM) is a rare malignancy with historically poor prognosis. Recent research has started to reveal increasingly prevalent genetic mutations seen in this malignancy. Here, we report a case of complete clinical remission of unresectable, metastatic MPeM with systemic chemotherapy. Immunohistochemistry of our patient's malignant cytology sample showed loss of Breast Cancer Gene 1-associated protein-1 expression (BAP1). The patient had synchronous diagnoses of primary squamous cell carcinoma of the anus, benign schwannoma and meningioma. Following the completion of 18 cycles of pemetrexed and bevacizumab, the patient has remained in clinical remission for 8 months. We examine the unusual susceptibility of unresectable MPeM to systemic chemotherapy and attribute susceptibility to the molecular milieu created by mutations in multiple DNA repair pathways. We encourage increased testing for and analysis of mutations in DNA repair pathways to improve future treatment outcomes in this rare malignancy.

BACKGROUND

Malignant peritoneal mesothelioma (MPeM) originates from serosal tissue lining the abdominal wall and is a rare malignancy with poor prognosis and treatment outcomes. While cytoreductive surgery and/or intraperitoneal chemotherapy improves survival for eligible patients, the overall survival after diagnosis is estimated to be 46% at 1 year and 20% at 5 years.[1–3] Cure of MPeM is rare, with only sporadic case reports of complete remission following cytoreductive surgery or intraperitoneal chemotherapy.[4 5] We present a case of complete clinical remission of unresectable, metastatic MPeM following systemic chemotherapy.

CASE PRESENTATION

The patient was a woman in her 60s with a remote history of meningioma and newly diagnosed squamous cell carcinoma (SCC) of the anus who initially presented to the medical oncology clinic after 6–12 months of rectal bleeding, weight loss, weakness and chronic constipation. Concurrently, she reported a 6- to 9-month history of memory problems, poor taste and smell, imbalance and abulia (figure 1). These neurological symptoms were later discovered to be from an 8 cm recurrent meningioma in the olfactory groove. She denied abdominal pain, abdominal fullness or ascites. Vital signs were within normal range. She ambulated with a wheelchair on her first office visit and had an Eastern Cooperative Oncology Group (ECOG) performance score of 2. The medical history consisted of bifrontal craniotomy and radiation for prior meningioma, chronic tinnitus and lower extremity neuropathy. She did not use tobacco, alcohol or illicit drugs. Her family history was positive for breast and colon cancer.

The patient experienced improvement in rectal bleeding, weight loss and chronic constipation following expeditious radiation therapy for SCC of the anus. However, 5 months after her initial presentation, the patient developed new symptoms of dyspnoea, palpitations and bilateral lower extremity oedema. Her symptoms began insidiously over a period of weeks but abruptly increased in severity prompting further medical workup.

INVESTIGATIONS

Initial skull-to-thigh positron emission tomography (PET)/CT showed avid fluorodeoxyglucose (FDG) uptake in the distal rectum consistent with known anal cancer, findings concerning metastases to the right external iliac node and an incidental non-specific FDG focus of the right lateral abdominal wall muscle (figure 2A,C). Subsequent biopsies determined the lesion of the right external iliac node to be a benign schwannoma and the lesion of the right lateral abdominal wall to be MPeM involving skeletal muscle and fibroadipose tissue. H&E staining of MPeM showed cords of epithelioid and rhabdoid cells, with ample eosinophilic cytoplasm and inconspicuous nucleoli involving the fibrous tissue (figure 3A). Immunohistochemistry stains of MPeM showed tumour cells to be strongly positive for cytokeratin AE1/AE3, calretinin and Wilms' tumor 1 (figure 3B–D) while negative for CDX-2, GATA-3, MOC-31, carcinoembryonic antigen monoclonal, BER-EP4 and p40.

The patient experienced no obvious symptoms related to the incidental MPeM at the time of diagnosis. However, 5 months after, repeat imaging was performed for new onset dyspnoea which showed increased FDG uptake of the mesothelioma as well as a large pericardial effusion. Cytology and tumour cell immunohistochemistry of the pericardial fluid were consistent with previous MPeM biopsy findings. Immunohistochemistry studies of the patient's cytology sample revealed loss of Breast Cancer Gene 1-associated protein-1 (BAP1) with the likely pathogenic variant BAP1 c.14G>Ap.W5* VAF: 52% chr3:g.52443881C>T (Tier 2C). Fluorescent in situ hybridisation showed retained CDKN2A and

To cite: Lee J, Turetsky J, Nasri E, *et al*. *BMJ Case Rep* 2023;**16**:e255916. doi:10.1136/bcr-2023-255916

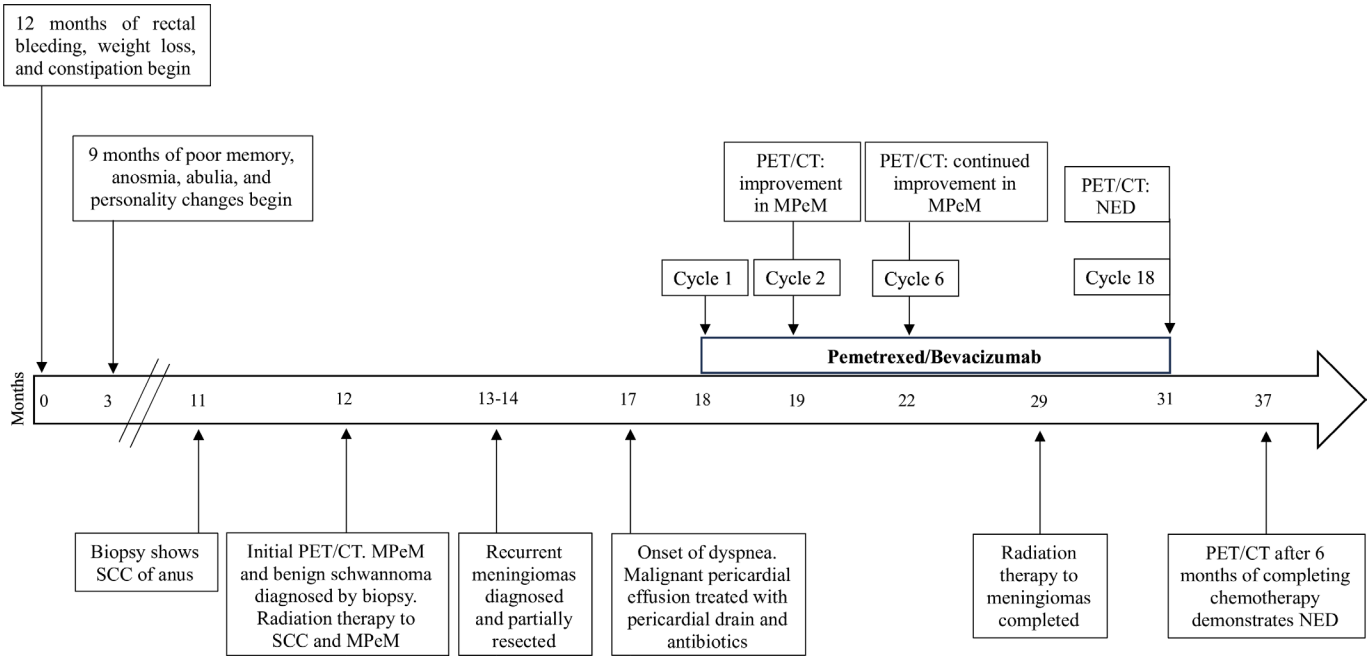

Figure 1 Timeline of symptoms, diagnoses and treatments. MPeM, malignant peritoneal mesothelioma; NED, no evidence of disease; PET/CT, positron emission tomography/computed tomography; SCC, squamous cell carcinoma.

NF2, all supporting the diagnosis of malignant mesothelioma metastatic from the peritoneum.

TREATMENT

The patient completed stereotactic body radiation therapy to the primary lesion at the time of MPeM diagnosis. Subsequent recurrence and metastatic spread resulted in hospital admission for management of infected pericardial effusion with pericardiocentesis and vancomycin. She was a poor surgical candidate for resection of MPeM due to metastatic presentation. Ultimately, the patient was stabilised and started on systemic pemetrexed and bevacizumab. The platinum agents included in the National Comprehensive Cancer Network's (NCCN) MPeM treatment guidelines (cisplatin or carboplatin) were withheld given the patient's history of longstanding tinnitus and lower extremity neuropathy.[6] Pembrolizumab was considered but was

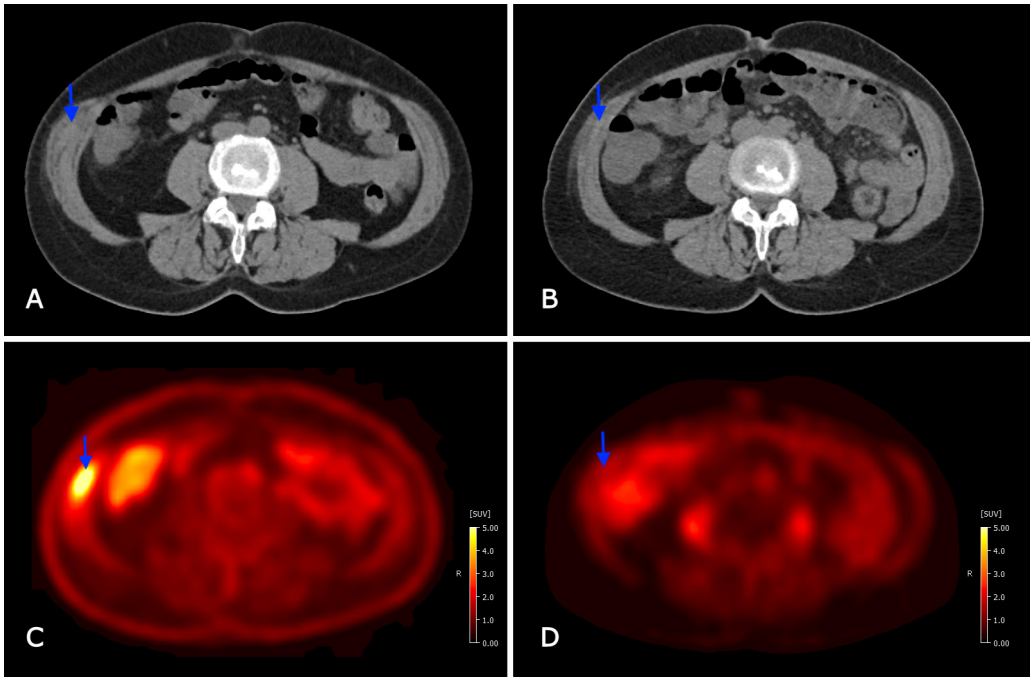

Figure 2 (A) Initial CT scan of abdominal wall showing invasion of mesothelioma into skeletal muscle and fibroadipose tissue. (B) CT scan of abdominal wall 6 months after completing chemotherapy showing resolution of mesothelioma. (C) Initial positron emission tomography (PET) scan of abdominal wall showing invasion of mesothelioma into skeletal muscle and fibroadipose tissue. (D) PET scan of abdominal wall 6 months after completing chemotherapy showing resolution of mesothelioma.

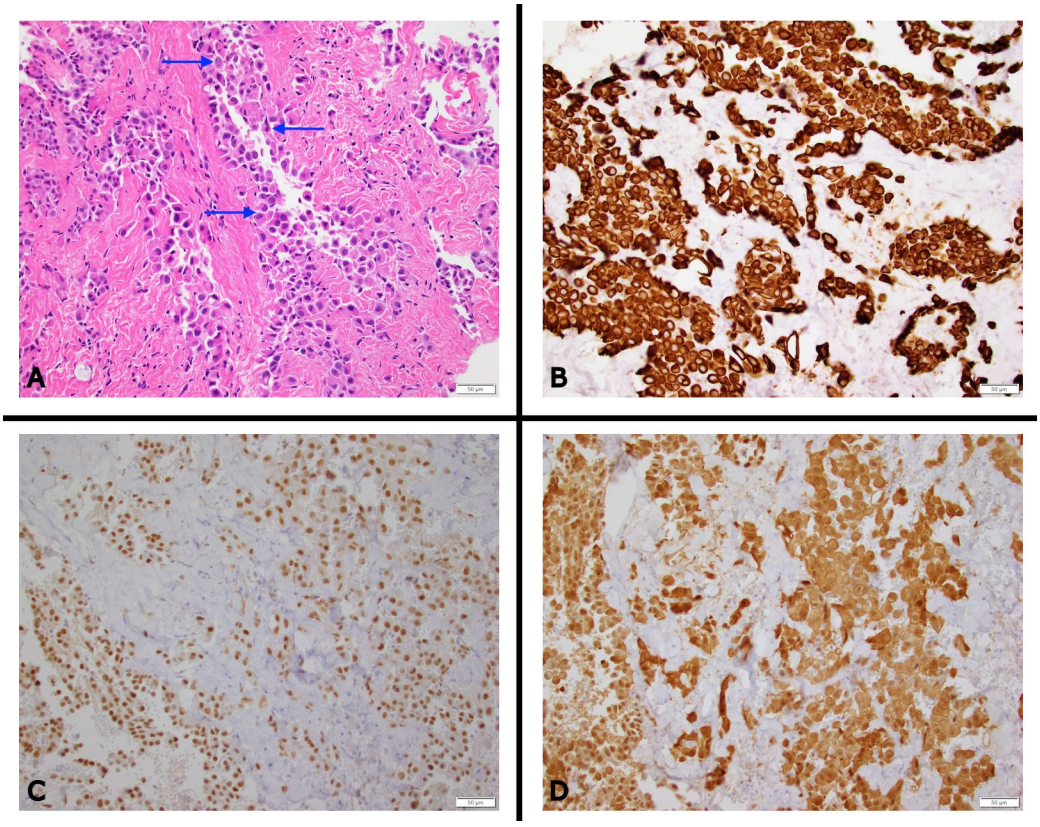

Figure 3 (A) H&E stain of mesothelioma showing cords of epithelioid and rhabdoid cells, with ample eosinophilic cytoplasm and inconspicuous nucleoli involving the fibrous tissue. (B) Immunohistochemical stain showing tumour cells to be strongly positive for cytokeratin AE1/AE3. (C) Immunohistochemical stain showing tumour cells to be strongly positive for calretinin. (D) Immunohistochemical stain showing tumour cells to be strongly positive for Wilms' tumor 1.

not approved by the patient's insurance. Over the course of 13 months, the patient received 18 cycles of pemetrexed 500 mg/m^2 and bevacizumab 15 mg/kg every 3 weeks.

OUTCOME AND FOLLOW-UP

PET/CT scan performed after completing 18 cycles of pemetrexed/bevacizumab showed no evidence of disease, and the patient remained asymptomatic. She remains on a treatment holiday for 8 months at the time of this report, with serial PET/CTs (figure 2B,D) revealing no definitive evidence of disease progression or metastatic disease. Her ECOG status after completing treatment and at the time of this report was 0.

Additionally, the patient remains without disease recurrence for anal SCC and meningioma following definitive local therapies. She has had two negative biopsies and rectal exams under anaesthesia for the SCC and continues with MRI surveillance after repeat resection and radiation for meningioma. No treatment was administered for the benign schwannoma.

DISCUSSION

The current NCCN treatment guidelines for unresectable MPeM indicate the paucity of patients who achieve remission, with stipulations for completing first-line systemic therapy followed by maintenance of bevacizumab until disease progression.[6] Our patient achieved clinical and radiological remission with PET/CT. While there are limitations with all imaging modalities in detecting peritoneal lesions,[7] others have demonstrated 100% sensitivity and 82% accuracy in detecting MPeM with PET/CT prior to treatment and during surveillance, respectively.[8] Another study specifically detected 12/14 patients with epithelioid peritoneal mesothelioma with PET prior to subsequent laparotomy.[9] These findings, in addition to serial negative PET/CTs and symptom resolution, support the use of PET/CT to evaluate treatment response. With imaging limitations in mind, previous reports have only demonstrated remission in patients who were candidates for cytoreductive surgery and/or received intraperitoneal chemotherapy.[4 5] These poor outcomes highlight the need to increase understanding of the underlying genetics and pathogenesis of MPeM to effectively treat the disease.

While MPeM shares the same histological subtypes (epithelioid, sarcomatoid and biphasic/mixed) with the more prevalent and well-studied malignant pleural mesothelioma (MPM), it remains a distinct clinical entity characterised by younger age of onset, weaker association with asbestos exposure and equal prevalence in men and women. Furthermore, the pathogenesis of MPeM is likely unique from its pleural form, with differences in genetic alterations and a greater proportion of patients affected by germline mutations.[10–12]

One such genetic alteration with prognostic and diagnostic implications in all MM is the BAP1 tumour suppressor gene. Located on chromosome 3 (3p21.1), BAP1 is involved in a multitude of cellular processes including transcriptional regulation, chromatin modulation and the DNA damage response pathway via homologous recombination repair (HRR) as well as the ubiquitin-proteasome pathway.[13–15] Recurrent germline and somatic BAP1 mutations have been identified in all MM; however, germline mutations are more common in patients with peritoneal disease, multiple malignancies and a family history

of mesothelioma, further supporting a molecular difference between MPeM and MPM.[12 16]

Several malignancies have been recognised along with mesothelioma as part of a disorder known as BAP1 tumour predisposition syndrome (BAP1-TPDS). The most strongly associated malignancies include mesothelioma, uveal and cutaneous melanomas, BAP1-inactivated melanocytic tumours and renal cell carcinoma.[15 17] Recently published practice guidelines supported an additional association for meningioma, but do not classify it as a core tumour in this syndrome. At this time, it is less clear if cholangiocarcinoma, hepatocellular carcinoma or other cancers are part of BAP1-TPDS.[17] Prior studies have shown improved prognosis in MM and associated malignancies in those with BAP1 mutations, but the mechanisms underlying this survival benefit are unclear.[16 18]

It is unknown if our patient had an underlying germline BAP1 mutation and/or BAP1-TPDS. The prevalence of BAP1 germline pathogenic variants is rare in population studies, especially in patients without a personal or family history of other core BAP1-associated tumours.[17] While it is theoretically possible to have a de novo germline BAP1 mutation wherein other family members are cancer-free, the incidence of this is low.[17 19] Germline testing, therefore, should be performed judiciously. Our patient did not have a family history of BAP1-associated tumours, but genetic testing could have been appropriate because she had peritoneal disease, no known asbestos exposure and meningiomas—all features supporting the likelihood of additional genetic alterations unique from sporadic or pleural forms of mesothelioma.[12] Germline next-generation sequencing was ordered, but ultimately was not completed by the patient.

Apart from BAP1, patients with MM also harbour other germline mutations that disrupt DNA repair pathways and cause known cancer syndromes—mutations in BRCA genes, TP53, MLH1 and more have been reported.[12] Somatic mutations of BAP1 are common as well, seen in over 60% of patients with MM.[16] Knowledge of these additional genetic alterations and the high prevalence of BAP1 mutations emphasises the need for increased germline testing, systematic data collection and analysis of pathological variants in MM to guide future treatment.

The presence of additional genetic alterations in MM may also provide insight regarding the clinical remission of our patient. Pemetrexed is an antifolate agent that uniquely inhibits three or more enzymes required for DNA synthesis and folate metabolism.[20] It is part of first-line treatment for MM but not considered targeted therapy. However, the role of BAP1 in HRR, similar to BRCA1, offers a plausible rationale for the effectiveness of targeted therapy in those with gene mutations. In breast and ovarian cancer, poly(ADP-ribose) polymerase inhibitors (PARPi) have proven to be effective in those with BRCA1 mutations by impairing a major alternative DNA repair mechanism for tumour cells in patients who are already deficient in HRR. Targeted therapy against vascular endothelial growth factor (VEGF)—by bevacizumab in our patient—in combination with PARPi has also been investigated given the effect of VEGF inhibition on BRCA1 expression; inhibition induces hypoxia in the tumour microenvironment, downregulating the expression of BRCA1 and subsequently impairing HRR.[21] Understanding of these targeted therapies in other cancers and observation of concomitant mutations in multiple DNA repair genes in MM have led to the investigation of PARPi in patients with MM and BAP1 mutations.

Preclinical studies have demonstrated synthetic lethality by markedly reducing replication in cell lines of MPM with PARPi.[22] A phase two clinical trial of the PARPi rucaparib in BAP1-deficient or BRCA1-deficient MM showed disease control rate of 58% at 12 weeks.[23] Another ongoing phase two clinical trial using the PARPi niraparib led to partial response or stable disease in 78% of patients with refractory metastatic tumours and BAP1 mutations.[24]

Due to the frequency of both somatic and germline mutations in MM, it is likely that other patients with unresectable MPeM treated with first-line therapy—pemetrexed, a platinum agent and bevacizumab—also harboured BAP1 mutations.[6] Therefore, the unique, chemotherapy-induced remission with pemetrexed and bevacizumab in our patient can likely be attributed to other genetic alterations in addition to the loss of BAP1 expression—perhaps additional mutations in BRCA1 or other DNA repair pathways. This conclusion is supported by the heterogeneity of findings from studies of PARPi in MM with BAP1 deletions. The preclinical study discussed above did show synthetic lethality of MPM cell lines, but this occurred regardless of BAP1 mutation status.[22] Moreover, a third phase two clinical trial studied the PARPi olaparib in MM patients with somatic and germline BAP1 mutations; when compared with those with wild-type BAP1, patients with germline mutations in this study actually had decreased overall survival and progression-free survival.[25] We believe that the incongruity between these studies and the clinical remission of our patient strongly suggests the interaction of multiple genetic alterations in patients with MPeM and BAP1 mutations. We recommend the need for increased and systematic efforts to test patients with MPeM for germline and somatic mutations in DNA repair pathways to improve our understanding of how these mutations interact and respond to treatment.

Learning points

- Malignant peritoneal mesothelioma is a distinct clinical entity with unique molecular features.
- Consider other BAP1-TPDS tumours when evaluating a patient with mesothelioma.
- Consider genetic testing in patients who have a personal or family history of multiple, core BAP1-TPDS tumours—this may help inform future genotype-phenotype correlations.
- New targeted therapies against malignant mesothelioma are being investigated, including PARP inhibitors in those with BAP1 mutations.

Contributors JL contributed to conceptualisation, investigation, writing of the original draft, reviewing and editing. JT contributed to radiology figure acquisition and interpretation, pathology figure formatting, reviewing and editing. EN contributed to pathology figure acquisition and interpretation, reviewing and editing. SCR contributed to conceptualisation, investigation, reviewing, editing and supervision.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests Dr Sherise C Rogers is a Medsphere consultant and Natera Oncology Advisor. She is also a recipient of the Robert A Winn Diversity in Clinical Trials Career Development Award, funded by Bristol Myers Squibb Foundation. There are no declared competing interests for any of the other authors.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iD
Jimmy Lee http://orcid.org/0009-0003-0789-8941

REFERENCES

1 Acs M, Gerken M, Gajic I, *et al*. Ten-year single-center experience with treatment of primary diffuse malignant peritoneal mesothelioma (DMPM) by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). *Langenbecks Arch Surg* 2022;407:3057–67.
2 Helm JH, Miura JT, Glenn JA, *et al*. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: a systematic review and meta-analysis. *Ann Surg Oncol* 2015;22:1686–93.
3 Ullah A, Waheed A, Khan J, *et al*. Incidence, survival analysis and future perspective of primary peritoneal mesothelioma (PPM): a population-based study from SEER database. *Cancers (Basel)* 2022;14:942.
4 Prorocic M, Vasiljevic M, Jankovic S, *et al*. Diffuse malignant peritoneal mesothelioma in a 31-year-old patient--case report. *Eur J Gynaecol Oncol* 2007;28:147–8.
5 Garcia Moore ML, Savaraj N, Feun LG, *et al*. Successful therapy of peritoneal mesothelioma with intraperitoneal chemotherapy alone. A case report. *Am J Clin Oncol* 1992;15:528–30.
6 National comprehensive cancer network. Mesothelioma: peritoneal. n.d. Available: https://www.nccn.org/professionals/physician_gls/pdf/meso_peritoneal.pdf
7 Patel CM, Sahdev A, Reznek RH. CT, MRI and PET imaging in peritoneal malignancy. *Cancer Imaging* 2011;11:123–39.
8 Domènech-Vilardell A, Rasiej MJ, Taub RN, *et al*. Clinical utility of 18F-FDG positron emission tomography in malignant peritoneal Mesothelioma. *Q J Nucl Med Mol Imaging* 2016;60:54–61.
9 Dubreuil J, Giammarile F, Rousset P, *et al*. The role of 18F-FDG-PET/ceCT in peritoneal mesothelioma. *Nucl Med Commun* 2017;38:312–8.
10 Carbone M, Adusumilli PS, Alexander HR Jr, *et al*. Mesothelioma: scientific clues for prevention, diagnosis, and therapy. *CA Cancer J Clin* 2019;69:402–29.
11 Hung YP, Dong F, Watkins JC, *et al*. Identification of ALK rearrangements in malignant peritoneal mesothelioma. *JAMA Oncol* 2018;4:235–8.
12 Panou V, Gadiraju M, Wolin A, *et al*. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. *J Clin Oncol* 2018;36:2863–71.
13 Yu H, Pak H, Hammond-Martel I, *et al*. Tumor suppressor and deubiquitinase Bap1 promotes DNA double-strand break repair. *Proc Natl Acad Sci U S A* 2014;111:285–90.
14 Ismail IH, Davidson R, Gagné J-P, *et al*. Germline mutations in Bap1 impair its function in DNA double-strand break repair. *Cancer Res* 2014;74:4282–94.
15 Murali R, Wiesner T, Scolyer RA. Tumours associated with Bap1 mutations. *Pathology* 2013;45:116–26.
16 Pastorino S, Yoshikawa Y, Pass HI, *et al*. A subset of Mesotheliomas with improved survival occurring in carriers of Bap1 and other Germline mutations. *J Clin Oncol* 2018;36.
17 Lalloo F, Kulkarni A, Chau C, *et al*. Clinical practice guidelines for the diagnosis and surveillance of Bap1 tumour predisposition syndrome. *Eur J Hum Genet* 2023;31:1261–9.
18 Baumann F, Flores E, Napolitano A, *et al*. Mesothelioma patients with germline Bap1 mutations have 7-fold improved long-term survival. *Carcinogenesis* 2015;36:76–81.
19 Walpole S, Pritchard AL, Cebulla CM, *et al*. Comprehensive study of the clinical phenotype of germline Bap1 variant-carrying families worldwide. *J Natl Cancer Inst* 2018;110:1328–41.
20 Adjei AA. Pharmacology and mechanism of action of pemetrexed. *Clin Lung Cancer* 2004;5 Suppl 2:S51–5.
21 Alvarez Secord A, O'Malley DM, Sood AK, *et al*. Rationale for combination PARP inhibitor and antiangiogenic treatment in advanced epithelial ovarian cancer: a review. *Gynecol Oncol* 2021;162:482–95.
22 Srinivasan G, Sidhu GS, Williamson EA, *et al*. Synthetic lethality in malignant pleural mesothelioma with Parp1 inhibition. *Cancer Chemother Pharmacol* 2017;80:861–7.
23 Fennell DA, King A, Mohammed S, *et al*. Rucaparib in patients with Bap1-deficient or Brca1-deficient mesothelioma (Mist1): an open-label, single-arm, phase 2A clinical trial. *Lancet Respir Med* 2021;9:593–600.
24 George TJ, Lee J-H, Hosein PJ, *et al*. Results of a phase II trial of the PARP inhibitor, niraparib, in Bap1 and other DNA damage response pathway deficient neoplasms. *JCO* 2022;40:3122.
25 Ghafoor A, Mian I, Wagner C, *et al*. Phase 2 study of olaparib in malignant mesothelioma and correlation of efficacy with germline or somatic mutations in *Bap1* gene. *JTO Clin Res Rep* 2021;2:100231.