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Case report

Cytology positive pericardial effusion causing tamponade in patients with high grade serous carcinoma of the ovary

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1. Introduction

High grade serous carcinoma (HGSC) of the ovary is known to cause malignant fluid accumulation in the peritoneal and pleural space. Reported but rare is malignant pericardial effusion with tamponade (Dracham et al., 2019). Urgent recognition and treatment of this rare condition is essential to lifesaving management. We present 3 cases of malignant pericardial effusion with features of cardiac tamponade caused by HGSC. Written informed consent was obtained from all patients presented in this report.

2. Case reports

2.1. Patient A

A previously healthy 41-year-old presented with an enlarged supraclavicular lymph node associated with non-specific abdominal symptoms. PET-CT demonstrated diffuse lymphadenopathy including supraclavicular, mediastinal, and carotid lymph nodes with a complex ovarian mass. Pathology of the biopsied supraclavicular lymph node demonstrated adenocarcinoma of ovarian primary. After an excellent response to 3 cycles of neoadjuvant carboplatin/paclitaxel, she was microscopically debulked. She received 6 cycles of adjuvant carboplatin/docetaxel due to a paclitaxel reaction. She is BRCA negative.

Disease recurred 6 months after chemotherapy with involved pelvic and paraaortic lymph nodes. A complete response was achieved with 6 cycles of liposomal doxorubicin but a second recurrence with abdominopelvic nodal disease was diagnosed 6 months later. She responded to 3 cycles of cisplatin/gemcitabine and then enrolled in a trial receiving rucaparib. After 32 cycles, she progressed and received 4 cycles of cisplatin/gemcitabine with one cycle of bevacizumab.

Nine months later, and 85 months after her original cancer diagnosis, she presented to emergency services with bloating, weakness, a change in bowel movements, and orthopnea. She was tachycardic at 128 beats/minute and hypotensive at 94/69 mmHg with remaining vital signs normal. A chest x-ray noted mildly enlarged cardiac silhouette and small bilateral pleural effusions (Fig. 1A). An electrocardiogram showed tachycardia, decreased QRS voltage, and non-specific T-wave changes. An echocardiogram showed a large pericardial effusion with features of tamponade. Pericardiocentesis was performed for 1 L and a pericardial drain remained in situ for 3 days (Fig. 1B). The pericardial and pleural fluid was positive for metastatic HGSC. On further imaging, she was noted to have a new pulmonary embolus, thrombi in the inferior vena cava, renal and portal vein, increased adenopathy, hepatic metastases, and peritoneal nodularity.

She was well following her 5-day hospital admission and 2 months on, is still without recurrence of her pericardial effusion and tolerating palliative single agent carboplatin.

2.2. Patient B

A 67-year-old with a history of type 2 diabetes, thalassemia minor, and breast ductal carcinoma in-situ presented with shortness of breath. She had a large pulmonary embolus, pleural effusions, peritoneal carcinomatosis, and ascites. Peritoneal and pleural cytology as well as omental biopsy were consistent with HGSC. She received 3 cycles of neoadjuvant carboplatin/paclitaxel. After a good response, she was microscopically debulked. She then received 6 cycles of adjuvant carboplatin/paclitaxel followed by 12 cycles of maintenance bevacizumab when she was noted to have recurred with omental nodularity and a

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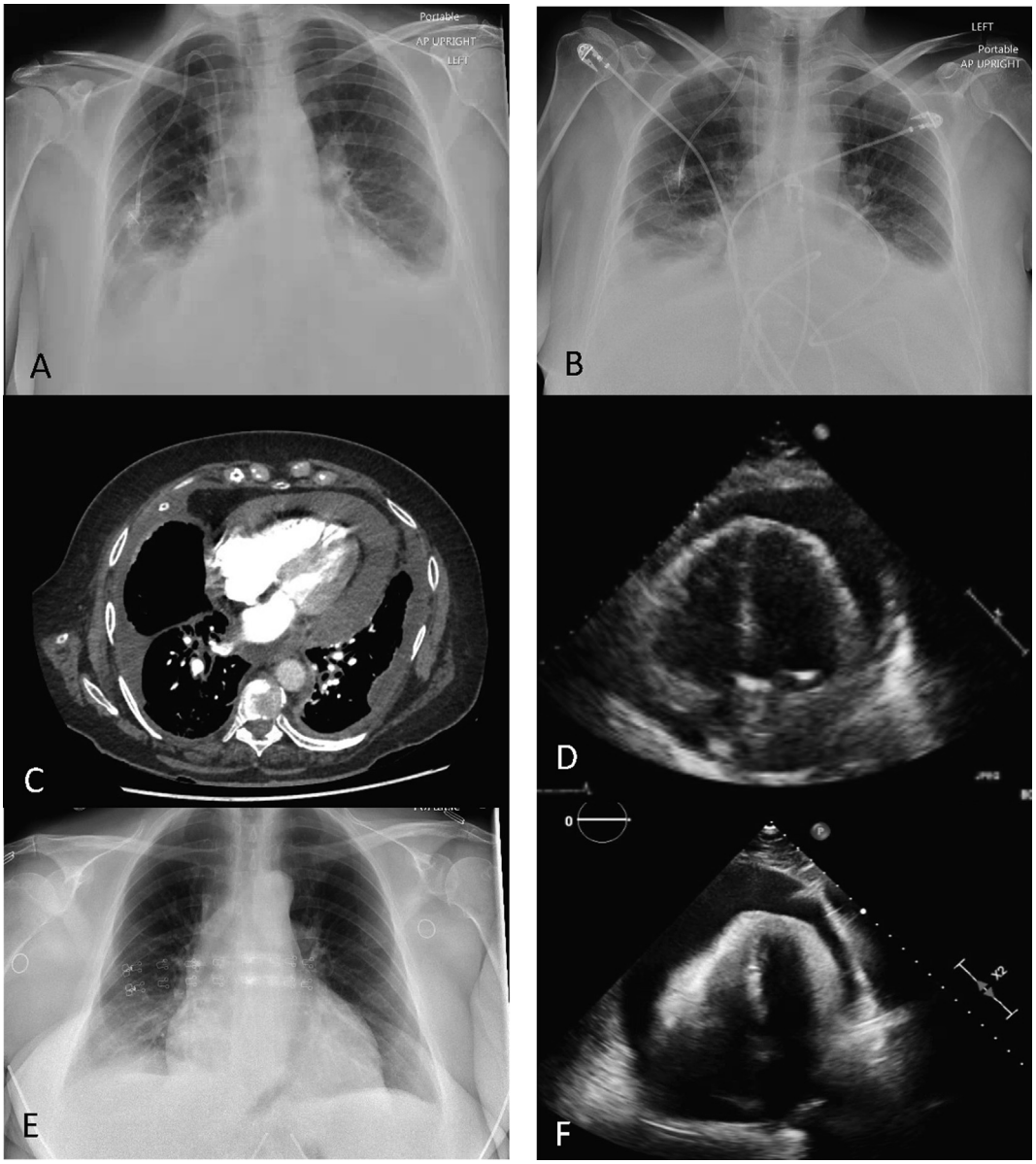

Fig. 1. Patient A – chest x-ray prior to pericardial drain (A) and chest x-ray after drain (B) Patient B – CT of pericardial effusion (C) and echocardiogram of pericardial effusion (D) Patient C – chest x-ray image prior to drain (E) and echocardiogram of pericardial effusion (F).

pleural effusion. She is BRCA negative.

Back on chemotherapy and 17 months after her initial cancer diagnosis, she developed increasing shortness of breath and O2 saturation of 75% on room air with otherwise normal vital signs. A CT showed both pulmonary embolism and pericardial effusion (Fig. 1C and D). Echocardiogram confirmed a large pericardial effusion with findings of tamponade. Pericardiocentesis was performed, a drain inserted, and a total of 930 cc of malignant fluid was drained. She received 3 cycles of cisplatin/gemcitabine with resolution of the effusion.

After a 4-month treatment break, she had progressive disease with pericardial thickening, new liver metastases, peritoneal carcinomatosis, mesenteric deposits, lymphadenopathy, and increasing pleural effusion. This improved with 4 cycles of cisplatin/gemcitabine. During treatment, she developed a repeat pulmonary embolism and small pericardial effusion not requiring drainage. Ten months after the malignant pericardial effusion, she is alive and on niraparib.

2.3. Patient C

A 56-year-old patient with osteoarthritis presented with abdominal pain and weight loss over 2 years. On CT scan, extensive enlarged paraaortic and prominent inguinal lymph nodes were seen. A retroperitoneal biopsy confirmed metastatic HGSC. She is BRCA negative. She underwent 3 cycles of neoadjuvant carboplatin/paclitaxel. After the first, she developed a right internal jugular vein clot from the brachiocephalic vein extending to the sigmoid sinus. She was microscopically debulked with intraoperative findings of a complete response. Three adjuvant cycles of carboplatin/paclitaxel were completed and a post-treatment PET-CT demonstrated no active disease. She recurred 17 months later in her inguinal lymph nodes and mesentery. After 3 cycles of carboplatin/paclitaxel followed by 2 cycles of carboplatin, she had a complete response. She recurred 7 months later with pelvic and inguinal adenopathy. She declined chemotherapy at that time as she was relatively asymptomatic.

Two months later, and 37 months after her cancer diagnosis, she presented to hospital with increasing dyspnea leading to presyncope

and orthopnea. A chest x-ray noted mild cardiac enlargement and an echocardiogram showed a large pericardial effusion with features of cardiac tamponade (Fig. 1E and F). A pericardial drain was left in situ for 24 h, draining a total of 1450 cc of bloody fluid, positive for HGSC.

She was started on palliative carboplatin within 2 weeks of her cardiac tamponade, and then transitioned to niraparib. Three months following pericardial tamponade, she is alive, tolerating treatment, and follow up imaging has shown no evidence of further pericardial effusion.

3. Discussion

Pericardial effusion develops most commonly due to iatrogenic, idiopathic, malignant, or infectious causes (Strobbe et al., 2017). If the fluid is of low volume or accumulates slowly, the effusion can be asymptomatic and found incidentally (Donato et al., 1986). Symptoms of effusion associated with tamponade include shortness of breath, chest pain and orthopnea. Physical exam findings include an elevated jugular venous pressure, quiet heart sounds, decreased blood pressure, narrow pulse pressure, and tachycardia. Investigations will often reveal an ECG with low QRS amplitude, an enlarged cardiac silhouette on chest x-ray, and an increase in pericardial fluid on CT chest or echocardiogram (Dracham et al., 2019; Donato et al., 1986). Among ovarian cancer patients who present with the above symptoms, more common diagnoses include pulmonary embolism, pleural effusion, or pneumonia. However, given the mortality risk with pericardial tamponade, it is an essential diagnosis to consider.

Malignancy is a major cause of pericardial effusion leading to tamponade (Strobbe et al., 2017). HGSC of the ovary is a very uncommon cause of cytology positive pericardial effusion. A retrospective study found that 1.2% of 255 patients reviewed developed a malignant pericardial effusion causing tamponade (Dauplat et al., 1987). Pericardial effusions are more common in lung and breast cancers (Dracham et al., 2019) and their pathophysiology includes lymphangitic, hematogenous, or local spread. Pericardial fluid drains through the subepicardial plexus to the mediastinal nodes. It is thought that metastasis to mediastinal lymph nodes spread via this lymphatic plexus to the heart, leading to malignant pericardial effusions (Donato et al., 1986).

A literature review of cytology confirmed pericardial effusions from recurrent HGSC of the ovary with descriptions of cancer treatment is presented in Table 1. Many published cases dating back to the 1980s and 1990s describe women who passed away within weeks to months of developing a pericardial effusion but significant changes in treatment protocols have occurred since that time. Limited literature is available on pericardial effusion associated with HGSC and its effects on treatment options and survival.

We report 3 additional cases of cytology positive pericardial effusions with tamponade presenting during the course of HGSC of the ovary. Our cases are unique for several reasons. Two of three patients initially presented with diffuse lymphadenopathy including one involving a supraclavicular node. This is an unusual initial presentation of HGSC of the ovary and the likely route of access to the pericardial space. The third patient had a more typical presentation of ovarian cancer with ascites, peritoneal disease, and pleural effusions. Each patient had a venous thromboembolism prior to or concurrently with the diagnosis of their pericardial effusion. Of the patients presenting with unusual lymphatic presentations, they also had unusual thromboembolism sites: renal and portal vein as well as involving the internal jugular vein.

To our knowledge, we report the second malignant pericardial effusion with tamponade in a patient previously treated with a poly ADP ribose polymerase (PARP) inhibitor. For this patient, without the benefit of the PARP inhibitor, it is likely her disease would have progressed more rapidly, perhaps never presenting with cardiac tamponade. Instead she had 85 months between diagnosis of cancer and pericardial

Table 1
Case reports of cytology positive high grade serous pericardial effusions with descriptions of patient cancer treatment and course.

Author	Age	Initial Stage	Time from Initial Diagnosis	Prior Lines of Therapy	Treatment for Effusion	Outcome
Dracham et al. (2019)	51	IIIC	7 years	Carboplatin/paclitaxel	Pericardiocentesis & pericardial window followed by carboplatin/paclitaxel then olaparib	Alive at time of publication 12 months post therapy
Feferkorn et al. (2014)	72	IIIC	6 years	Unspecified neoadjuvant and adjuvant chemotherapy, olaparib	Pericardiocentesis, patient refused chemo & recurred 6 weeks later & received a pericardiocentesis	Deceased after 6 weeks
Petersen et al. (2009)	Not reported	IV	Not reported	Topotecan/carboplatin, carboplatin/paclitaxel, bortezomib, temozolomide, liposomal doxorubicin	Pericardiocentesis & placement of a drain, recurred in 9 days & treated with repeat drain & sclerosis	Deceased after 12 months
Blich et al. (2007)	74	Not reported	Not reported	Doxorubicin/5FU/cyclophosphamide, liposomal doxorubicin	Pericardiocentesis & recurred 1 month later followed by another pericardiocentesis	Deceased after 1 week
Levitan et al. (1990)	46	IIIC	3 years	Cyclophosphamide/Adriamycin/Cisplatin	Pericardiocentesis & drain, tetracycline sclerosis followed by radiation to pericardium, cyclophosphamide/cisplatin	Deceased after 2.5 years
Mäenpää et al. (1988)	67	IIB	2 years	Cyclophosphamide/doxorubicin/tegafur	Pericardiocentesis followed by cyclophosphamide/doxorubicin/cisplatin	Deceased after 7 months
Lund (1985)	53 & 60 (2 patients)	III & IV	2 years	Doxorubicin/5FU /cyclophosphamide, cisplatin/hexamethylmelamine, & doxorubicin /5FU /cyclophosphamide,cisplatin/hexamethylmelamine	Pericardiocentesis, tetracycline sclerosis twice, recurred 2 weeks later. Repeat pericardiocentesis & drain. Effusion recurred in 1 week	Deceased after 1 week & Deceased after 3 months

tamponade.

All patients had pericardial drains inserted but none required sclerotherapy. None have had clinically significant re-accumulation of their effusion. Perhaps reflecting their younger ages, all patients had a performance status that allowed provision of palliative chemotherapy to reduce the likelihood of further fluid accumulation.

4. Conclusion

Cytology positive pericardial effusion and tamponade in HGSC of the ovary remains rare. We postulate that this presentation may become more common with advances in treatment such as PARP-inhibitors and hyperthermic intraperitoneal chemotherapy (HIPEC) that better control abdominal disease, permitting cancer growth in cavities not typically seen before. These cases add to the literature in their unique initial disease presentation and provide further prognostic information that pericardial effusions are not necessarily a perimortem event; and with prompt diagnosis and treatment, patients can have a prolonged life expectancy and improved quality of life.

5. Contributions

All authors reviewed the article for its content and editing. JK formulated the idea for the case report and contributed to the literature review, data collection, preparation, and editing of the article as well as care for the patients. RF refined the report direction and contributed to the literature review, data collection, preparation, and editing of the article as well as care for the patients. GN is responsible for one patient's management and contributed to the review and editing of this article. PC is responsible for two patients' management and contributed to the review and editing of this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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