CASE REPORT

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Niraparib-Associated Pulmonary Embolism in a Patient with BRCA Mutant Ovarian Cancer

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ABSTRACT Among the histological subtypes of ovarian cancer, high-grade serous ovarian carcinoma is the type most commonly associated with breast cancer 1/2 (BRCA1/2) mutations. The combination regimen of platinum and taxane is the first-line treatment for advanced ovarian cancer. Maintenance therapy with poli-ADP riboz polimeraz inhibitors (PARPi), with or without bevacizumab, is recommended for patients with BRCA1/2-wt/homologous recombination deficiency-positive or BRCA1/2 mutations tumors who achieve a complete or partial response to first-line platinum-paclitaxel chemotherapy following the completion of chemotherapy. The most common side effects associated with the use of PARPi are hematologic toxicities. In our case, we aim to present a rare case of pulmonary thromboembolism associated with approximately 23 months of niraparib use. Pulmonary thromboembolism should be considered in patients with respiratory symptoms when prescribing PARPi.

Keywords: PARP inhibitors; pulmonary embolism; ovarian neoplasms

Among the histological subtypes of ovarian cancer, high-grade serous ovarian carcinoma is the type most commonly associated with breast cancer 1/2 (BRCA1/2) mutations.[1] The combination regimen of platinum and taxane is the first-line treatment for advanced ovarian cancer.[2] Maintenance therapy with poli-ADP riboz polimeraz inhibitors (PARPi), with or without bevacizumab (Roche, CH), is recommended for patients with BRCA1/2-wt/homologous recombination deficiency-positive or BRCA1/2 mutations tumors who achieve a complete or partial response to first-line platinum-paclitaxel (BMS, USA) chemotherapy following the completion of chemotherapy.[3] The most common side effects of PARPi are hematological toxicity and gastrointestinal side effects, which are generally manageable. We present a rare case of pulmonary embolism associated with niraparib (GSK, UK) in a patient with high-grade serous ovarian carcinoma who has been on niraparib for approximately twenty three months.

CASE REPORTS

A 63-year-old female patient was diagnosed with triple-negative breast cancer in 2013 and received adjuvant therapy. During follow-up, 8 years after the initial diagnosis, elevated CA 125 levels of 1946 U/mL (normal range: 0-35) and CA 15-3 levels of 300 U/mL (normal range: 0-26) were detected. Further investigations revealed intra-abdominal implants, leading to suboptimal debulking surgery. The patient was diagnosed with high-grade serous ovarian carcinoma. The patient received platinum-based chemotherapy as first-line treatment, achieving a partial response.

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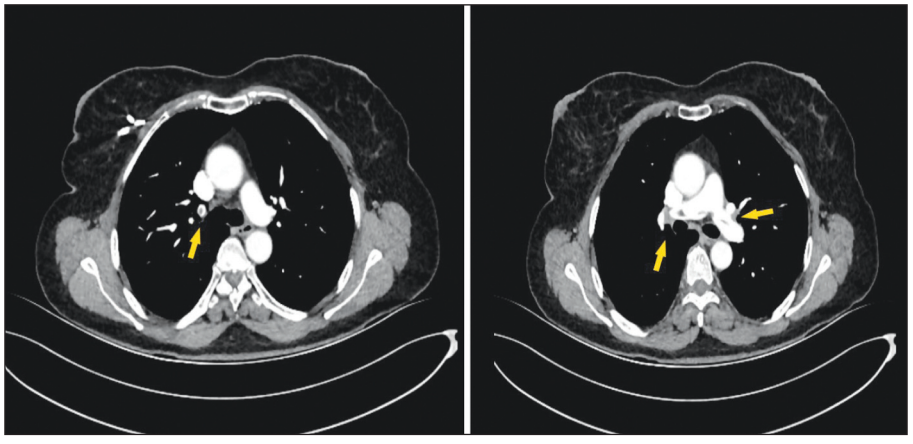

FIGURE 1: Filling defect consistent with embolism extending from both main pulmonary arteries to the right upper lobar and segmental branches, as well as the left lower lobar and segmental branches

Maintenance therapy with a PARPi was planned due to the detection of a BRCA2 germline mutation. Two months after completing chemotherapy, treatment with niraparib was initiated at a dose of 200 mg once daily, resulting in a complete response. Twenty three months after starting niraparib, a routine chest computed tomography scan revealed filling defects in both main pulmonary arteries consistent with pulmonary embolism. The patient's D-dimer level was elevated at 1.11 mg/L (0-0.55), and imaging findings were consistent with embolism (Figure 1), leading to a diagnosis of niraparib-associated pulmonary embolism. Doppler ultrasound revealed deep vein thrombosis in the right lower extremity. We paused niraparib treatment for 2 weeks and initiated anticoagulant therapy. During follow-up and treatment, no symptoms of pulmonary embolism were observed.

Informed consent was obtained from the patients for the publication of the case image and accompanying images.

DISCUSSION

The standard treatment for ovarian cancer includes maximum debulking surgery followed by 6 cycles of platinum-paclitaxel combination chemotherapy. The recurrence rate is high in these patients. The 5-year overall survival rate for patients diagnosed with advanced ovarian cancer is between 26% and 42%.[4] PARPi play a role in the repair of single-strand DNA breaks and in transcription regulation. PARPi represent a new treatment option for cancers known to have underlying mechanisms of DNA repair deficiencies, such as ovarian cancer.[5] Niraparib, olaparib (Astrazeneca, UK), and rucaparib (Gmblt, Austria) are approved for maintenance therapy in platinum-sensitive advanced ovarian cancer patients and significantly prolong progression-free survival.

Among the PARPi options, olaparib is typically administered at 300 mg twice daily (every 12 hours), and niraparib is given once daily at 200-300 mg. Due to the common side effect of thrombocytopenia, the initial dose of niraparib is determined based on platelet count and the patient's weight.

PARPi are associated with cardiovascular adverse events such as thromboembolic events, and pulmonary embolism. The pathogenesis of cardiac toxicity is unknown and is thought to be associated to off-target effects involving the inhibition of non-target proteins.[6] Niraparib is most frequently related to hypertension and cardiovascular toxicity.[7]

Niraparib may interfere with dopamine and norepinephrine metabolism through off-target effects.[7,8] It inhibits the intracellular uptake of dopamine and norepinephrine by blocking the dual-specificity tyrosine phosphorylation-regulated kinase 1A. This leads to increased levels of these neurotransmitters, which can cause hypertension due to their positive inotropic effects on the heart.[7-9]

By Palazzo et al. PARPi-based therapies were related to a higher risk of any grade of pulmonary embolism compared to controls [fixed-effects model, RR=1.69, 95% Confidence interval (CI) 1.14-2.52; p=0.009].[10] In an analysis of nineteen studies including, the incidence of any grade of thromboembolic events was 2.6% in the control group, compared to 4.1% in the PARPi group. In the comparison between PARPi-based therapy and the control group, thromboembolic events were observed at a higher rate in the group receiving PARPi (Peto fixed-effects model, Peto odds ratio=1.49, 95% CI 1.14-1.95; p=0.004).

PARP inhibitor-based therapies are thought to be related to an increased risk of major adverse cardiovascular events, hypertension, thromboembolic events, and pulmonary embolism.[10] Patient-specific risk factors (e.g., prior anthracycline-based chemotherapy or hormone therapy like tamoxifen (Astrazeneca UK) in breast cancer, or high thromboembolic risk in pancreatic cancer) should be identified, and monitoring and control of these side effects should be taken into account.

In the patient receiving niraparib treatment, who showed an embolic defect on imaging, no underlying factors that could facilitate embolism such as active chemotherapy, recent surgery, infection, or immobilization were present. Therefore, niraparib-related pulmonary embolism was considered in our case. However, pulmonary embolism is not included among the known side effects or rare complications of niraparib. A similar case has been reported in the literature, while the precise mechanism behind this remains unknown, it is important to consider the possibility of niraparib-associated pulmonary embolism in patients presenting with symptoms like shortness of breath and fatigue while on niraparib therapy.[11]

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Aysun Fatma Akkuş, Sernaz Topaloğlu, Muhammet Bekir Hacıoğlu;* ***Design:*** *Aysun Fatma Akkuş, Bülent Erdoğan, Gökhan Öztürk;* ***Control/Supervision:*** *Aysun Fatma Akkuş, Sernaz Topaloğlu, Muhammet Bekir Hacıoğlu, Bülent Erdoğan;* ***Data Collection and/or Processing:*** *Aysun Fatma Akkuş, Gökhan Öztürk, İsmail Bayrakçı;* ***Analysis and/or Interpretation:*** *Aysun Fatma Akkuş, Muhammet Bekir Hacıoğlu, Gökhan Öztürk;* ***Literature Review:*** *Bülent Erdoğan, Sernaz Topaloğlu, Gökhan Öztürk;* ***Writing the Article:*** *Aysun Fatma Akkuş, Muhammet Bekir Hacıoğlu, Sernaz Topaloğlu;* ***Critical Review:*** *Muhammet Bekir Hacıoğlu, Bülent Erdoğan, Sernaz Topaloğlu;* ***Materials:*** *Gökhan Öztürk, İsmail Bayrakçı, Sernaz Topaloğlu.*

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