# Unusual Ovarian Cancer Relapse Managed by Nivolumab in a Long-term Surviving Patient with PD-L1 Mutation

**Jie Yang, Jun-Jun Yang, Jun Zhao, Tong Ren, Feng-Zhi Feng, Xi-Run Wan, Yang Xiang**

Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Beijing 100730, China

**Key words:** Extra Peritoneal Metastasis; Long Survival; Nivolumab; Ovarian Cancer; Programmed Death-ligand 1

## Introduction

This report describes a case of ovarian cancer recurrent as sternal and costal metastasis long after initial treatment. The whole-exome sequencing suggested programmed death-ligand 1 (PD-L1) mutation. The patient responded well to nivolumab, an anti-PD-1 monoclonal antibody. We discuss the case and review the literature.

## Case Report

This report is approved by the Institutional Review Board of Peking Union Medical College Hospital. A 70-year-old female with acute abdomen referred to our hospital and received an emergency laparoscopic exploration in July 2008. Right inguinal hernia with small intestine protrusion was found, as well as ascites with peritoneal dissemination and large omental cake. Although bilateral ovaries were grossly normal, biopsy of both ovaries and peritoneal was done in addition to hernia repair. Pathology examination demonstrated serous papillary carcinoma in both ovaries. Two cycles neoadjuvant chemotherapy of taxol and carboplatin (TC, taxol 175 mg/m$^2$, carboplatin area under the curve = 5, every 3 weeks) were added. Subsequently, a comprehensive cytoreductive surgery was performed. Surgical pathology examination established a Stage IIIc ovarian serous papillary carcinoma. The patient received another six cycles of TC chemotherapy, during which the CA125 level slopped from 1010 to normal after 2 cycles of postoperative chemotherapy. Then, she was under regular surveillance without any sign of relapse till the 7$^{th}$ year in 2015; a tender mass was palpated at the right sternocostal region. PET-CT demonstrated a 3.7 cm × 4.8 cm soft-tissue mass with high standardized uptake values (SUV) in anterior mediastinum. Thoracotomy and lower sternum resection were performed and pathology revealed poorly differentiated adenocarcinoma with immunohistochemistry compatible with ovarian cancer metastasis. Thoracic radiation was added as well as four courses of taxol chemotherapy. Platinum was omitted due to late onset allergy of carboplatin. CA125 level remained normal after the initial treatment. Seven months later, the patient noticed a fixed protuberance of 2 cm in diameter on her left forehead. Cranial magnetic resonance imaging demonstrated left parietal and frontal bone osteolytic osseous metastasis. PET/CT showed multiple nodules in both lungs with high SUV as well as the eighth posterior rib, right sacral bone, and left frontal bone, which highly indicated cancer metastasis. The patient received cranial radiation and zoledronic acids for osteolytic osseous metastasis. The whole-exome sequencing revealed CD274 (PD-L1), JAK2, and PDCD1LG2 (PD-L2) gene amplification and functional loss of p53 due to pretermination of transcription. Thus, nivolumab was administered at a dosage of 3 mg/kg every 2 weeks for seven cycles. Five months later, cranial MRI revealed regression of subcutaneous involvement on left frontal bone leaving bone erosion, and pulmonary metastases were also greatly relieved in CT examination [Figure 1].

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**Address for correspondence:** Prof. Yang Xiang, Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital, Beijing 100730, China
E-Mail: xiangy@pumch.cn



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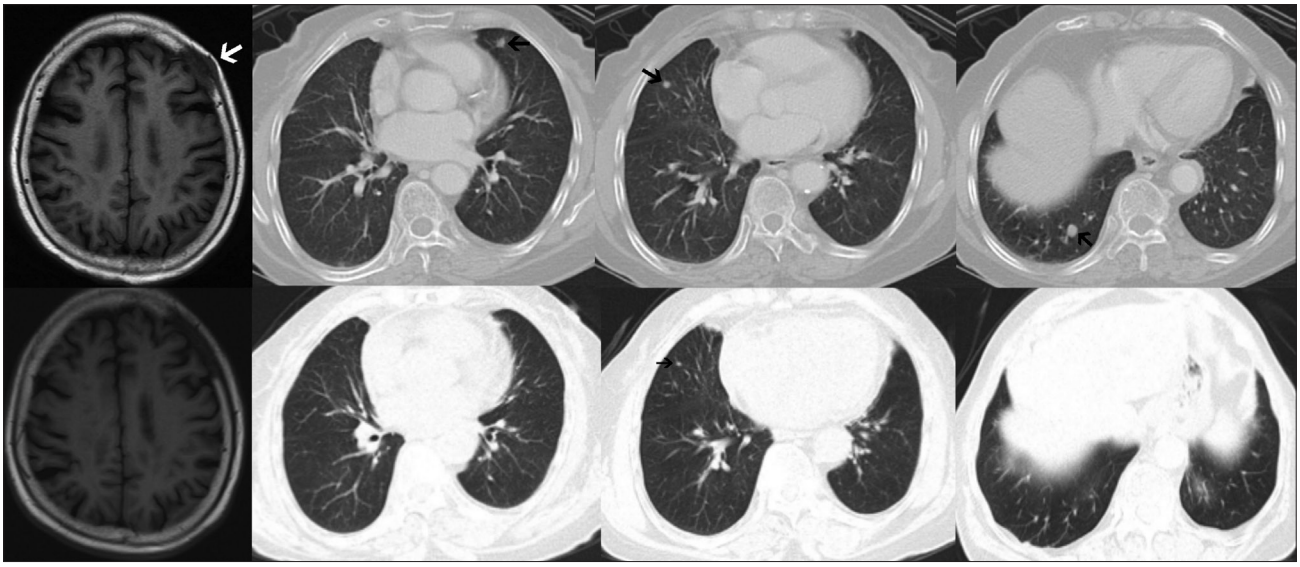

**Figure 1:** Comparison of cranial and lung tumor nodules before (upper) and after (lower) the treatment of programmed death-ligand 1 antibody. Subcutaneous involvement of left frontal bone was nearly complete remission leaving bone erosion and pulmonary nodules were also greatly regressed after seven courses of nivolumab.

The patient reported no adverse effects and received image evaluation 11 months after all the treatments.

## Discussion

The ovarian cancer metastasis to bones remains a relatively uncommon clinical scenario; the thoracic wall and extraperitoneal bone metastasis are considered to be extremely rare. This patient presented a very good response to initial treatment with an atypical late-term recurrent pattern as solitary thoracic wall metastasis. The incidence of bone involvement in ovarian cancer has been reported less than 4%. A postmortem study reviewed 73 ovarian cancer patients; 15% autopsy results showed bone involvement including the pelvis, vertebrae, femur, and skull.[1] Bone metastasis was generally considered through systemic hematogenous route, which usually occurred in late stage of ovarian cancer. Nevertheless, no involvements of the sternum or the costae have been described in these series.[1] Systemic hematogenous metastasis is generally considered the main route for distant thoracic metastasis. Another possible route for this kind of metastasis was by abdominal lymph system.

This patient expressed PD-L1/2 and JAK2 mutation. PD-1, an immune checkpoint receptor expressed by T-cells, binds to its ligands and suppresses antigen-specific cancer immune reactions. Genetic studies in lung cancer found that an increase of the copy number of the PD-L1 gene was accompanied by an increase of JAK2 gene, which further enhanced PD-L1 protein expression.[2] Webb *et al*. reported that PD-L1 expression was a favorable prognostic feature of high-grade serous ovarian cancer.[3] A Phase II clinical trial used the nivolumab, a human immunoglobulin G4 anti-PD-1 receptor-blocking monoclonal antibody, to treat platinum-resistant, recurrent, or advanced ovarian cancer and showed encouraging safety and clinical efficacy. This patient was over 70 years old and allergy to platinum. In consideration for the relatively low effect and high adverse effect of second-line chemotherapy, in addition to the PD-L1 mutation revealed by gene sequencing, we decided to use zoledronic acids for maintenance of osteolysis and anti-PD-1 monoclonal antibody to ensure the quality of life. The patient showed a promising response to these multimodality treatments. Management of atypical recurrent ovarian cancer remains highly controversial and personalized. Multimodality treatment such as systemic chemotherapy, radiation, and even molecular-targeted therapy may be useful in tumor control.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initial will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.


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Nil.


### Conflicts of interest

There are no conflicts of interest.

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