Two cases of rare late onset life-threatening pseudoprogression with immune check point inhibitors in advanced cancer patients – a case report

Valentin Coudert, Yves-Marie Robin, Williams Tessier, Alexandra Forestier & Nicolas Penel

To cite this article: Valentin Coudert, Yves-Marie Robin, Williams Tessier, Alexandra Forestier & Nicolas Penel (2021) Two cases of rare late onset life-threatening pseudoprogression with immune check point inhibitors in advanced cancer patients – a case report, Acta Oncologica, 60:5, 683-686, DOI: 10.1080/0284186X.2021.1885060

To link to this article: https://doi.org/10.1080/0284186X.2021.1885060

View supplementary material

Published online: 13 Feb 2021.

Submit your article to this journal

Article views: 432

View related articles

View Crossmark data
Two cases of rare late onset life-threatening pseudoprogression with immune check point inhibitors in advanced cancer patients – a case report

Valentin Coudert, Yves-Marie Robin, Williams Tessier, Alexandra Forestier and Nicolas Penel

Medical School, Lille University, Lille, France; Biopathology Department, Centre Oscar Lambret, Lille, France; Laboratoire « Protéomique, Réponse Inflammatoire et Spectrométrie de Masse » (PRISM), Inserm U1192, Lille University, Villeneuve d’Ascq, France; Surgery Department, Centre Oscar Lambret, Lille, France; Medical Oncology Department, Centre Oscar Lambret, Lille, France

ARTICLE HISTORY
Received 18 January 2021; Accepted 29 January 2021

Introduction
Administration of immune checkpoint inhibitors (ICIs) induces different patterns of response, including the classical complete or partial response and disease progression and new patterns such as hyperprogression and pseudoprogression. Pseudoprogression is defined as an increase in tumor size followed by a response to treatment, resulting from an exacerbated immune cell infiltration in the tumor bed, including CD103+ and CD8+ cells [1]. Pseudoprogression is a rare phenomenon, with a rate not exceeding 10% in patients treated with ICI [2]. In everyday practice, the misclassification of pseudoprogression as disease progression remains a concern. According to iRECIST guidelines, confirmation of the progression with later imaging is mandatory to make sure that the ‘unconfirmed’ progression is ‘disease progression’ and not ‘pseudoprogression’ [3]. Hodi et al. [4] described that pseudoprogression occurs more often at the beginning of ICI treatment. Here, we report two cases of dramatic pseudoprogression occurring 36 and 10 months after the initiation of ICI.

Case reports
Case report 1
A 44-year-old man with no medical history was diagnosed with high-grade renal cell carcinoma in 2011. He was initially treated with right radical nephrectomy. Six months later, a local recurrence was treated by surgery. In 2012, a new local recurrence was treated with sunitinib. In 2013, because of disease progression (appearance of one liver metastasis), the patient received second-line treatment with sorafenib. A few months later, because of stable disease, the patient underwent hepatectomy and resection of the local recurrence. Systemic treatments were then discontinued until April 2014, when pancreatic metastasis was diagnosed. Due to stable disease, the patient underwent a duodenopancreatectomy in August 2014. Two more surgical procedures were performed in February 2015 and May 2016 for the management of local relapse in the primary surgical bed. In March 2017, multiple bilateral lung metastases were diagnosed, and treatment was initiated with an ICI (nivolumab 3 mg/kg every 2 weeks). In May 2017, after a seizure, brain metastasis was diagnosed and treated with stereotaxic radiotherapy. Nivolumab was then resumed. The patient experienced a partial response and good quality of life. In October 2018, progression was found in lung metastases and treated with stereotaxic radiotherapy. Nivolumab was then resumed. A second pulmonary progression was found in November 2019 and required stereotaxic surgery. From March 2017 to March 2020, the patient received 70 cycles of nivolumab. In April 2020, the patient described loss of appetite, asthenia, pruritus, and pain in the right flank. A computed tomography (CT) scan showed a necrotic mass in the primary surgical bed, and this was consistent with a local relapse (Figure 1(A,B)). However, a few days later, a cutaneous fistula was observed in the right flank with a risk of colonic fistula, requiring an emergency surgical procedure. There was no fever, and the C-reactive protein level was within the normal range. The surgical specimen contained only necrotic tissue with immune cell infiltration (chronic inflammatory lymphocytic and macrophagic infiltrate), and there was no residual tumor cell (Figure 2(A)). These findings were consistent with pseudoprogression. After the surgery, the patient healed slowly and was in a good condition. In November 2020, we observed progression of lung metastases without local relapse.

Case report 2
A 74-year-old woman with medical history of hypertension and hypothyroidism was diagnosed with high-grade endometrial adenocarcinoma in 2014. She was initially treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy, four cycles of adjuvant chemotherapy (carboplatin–paclitaxel) and pelvic radiotherapy. At the end of the adjuvant radiotherapy, adrenal and peritoneal metastases were diagnosed and treated with subsequent lines of chemotherapy (liposomal doxorubicin, then weekly paclitaxel, then weekly epirubicin) without clinical benefit. In July 2016,
the mismatch repair (MMR) test showed the microsatellite
instability-high (MSI-H) phenotype, leading to the initiation
of treatment with an ICI (pembrolizumab 200 mg every
3 weeks). At the time, the extent of the disease was diffuse
peritoneal metastases and massive pelvic and retroperitoneal
lymph nodes. After initiation of therapy, the best response
was shrinkage of diffuse peritoneal metastases and retroperi-
toneal lymph nodes and stable disease of the peritoneal
mass. However, her general condition improved with a good
quality of life. In May 2017, after 17 cycles of pembrolizumab,
the patient experienced severe pelvic pain and the pelvic
skin was inflamed. The peritoneal mass was found to be nec-
rotic, with a risk of skin fistula. C-reactive protein level was
abnormal, twice the upper limit of normal. CT scan showed a
slight increase in pelvic mass size (179 mm compared to
134 mm in January 2017) (Figure 1(C,D)). The patient under-
went palliative surgery with the removal of this mass in May
2017. The surgical specimen contained chronic inflammatory
lymphocytic infiltration surrounding undifferentiated adenocarcinoma cells in the peritoneal mass and complete patho-
logical response in the lymph nodes. (Figure 2(B)). These
findings were consistent with pseudoprogression. Pembrolizumab was discontinued. CT scans in November
2017 and January 2018 demonstrated complete response.

This complete response was maintained until October 2020
without further treatment.

Discussion

We here report for the first time two cases of late-onset
life-threatening pseudoprogression requiring emergency
surgery with histopathology of the surgical specimens. In
both cases, pseudoprogression occurred after several
months of ICI treatment (36 and 10). The pseudoprogres-
sions were symptomatic with pain and inflamed skin. There
was no fever. The pseudoprogressions occurred in the sur-
gical bed of the primary tumor. At the metastatic sites, we
observed stable disease (case 1) or partial response (case 2).
In both cases, there was a slight increase in the size of the
primary site tumor. CT scans did not find specific patterns
suggesting pseudoprogression, excluding the fact that both
masses were necrotic. In both cases, we observed symptom-
atic pseudoprogressions requiring emergency surgery to
avoid fistulation. The risk-benefit ratio of surgery in the con-
text of heavily pretreated, advanced cases was discussed
extensively with surgeons, anesthesiologists, patients, and
families. In both cases, we discussed two opposite
approaches: symptomatic surgery of pseudoprogression

Figure 1. An increase in the size of a necrotic mass in the surgical bed of the primary tumor with cutaneous fistula in the right flank on computed tomography
(CT) scan for restaging in April 2020 (B) compared to that in January 2020 (A) in case 1, and an increase in the size of a necrotic peritoneal carcinomatous mass
with cutaneous infiltration in October 2017 (D) compared to that in January 2017 (C) in case 2.
versus palliative care. Decision making had to be done under pressure, without a definitive diagnosis (progression versus pseudoprogression). Biopsies may have been helpful; however, with the risk of fistulation, biopsies of these necrotic masses were deemed to be inappropriate. In conclusion, only the pathological report confirmed the diagnosis of pseudoprogression. As previously reported [5], pathological examination revealed that the increase in lesion size was likely due to massive lymphocytic infiltration in both cases, and complete pathological response without cancer cells was observed in one case.

Pseudoprogression is an atypical pattern of response. In some cases, it could be associated with dramatic symptoms, such as tamponade and pleural effusions [6], intracranial hypertension [7], or bowel perforation [8]. As in our two cases, pseudoprogression may also be late-onset after ICI initiation [9,10]. The severity of some clinical presentations and the misdiagnosis of pseudoprogression as disease progression could lead to inappropriate decisions such as discontinuation of ICI, contraindication to local treatment for managing complications of pseudoprogression, or referral to palliative care for treatment [11]. Recognizing pseudoprogression is of major importance since in most cases, it is followed by long-term disease control [12]. Radiographic follow-up, biopsy, histologic examination of enlarged lesions, circulating tumor DNA, and serum interleukin-8 levels may help diagnose pseudoprogression [13], underlining the need for a multidisciplinary approach for its management.

Conclusion

Physicians must be aware of the potential severe clinical presentation associated with pseudoprogression and the fact that new lesion appearance or growth of known lesions may not always signify a failure of disease control during ICI treatment. Indeed, as we observed in these two cases, pseudoprogression can occur after several months of ICI treatment.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Disclosure statement

No authors report any conflict of interest.

Informed consent

Both patients have provided informed consent for publishing their medical history and personal medical data (M004; deliberation n° 2018-155 on the 3rd May 2018).

ORCID

Valentin Coudert http://orcid.org/0000-0002-8051-3185

References

