CASE REPORT

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Is High White Blood Cell Count an Adverse Drug Reaction of PD-1 or Paraneoplastic Syndrome? A Case of Adenocarcinoma of the Lung

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ABSTRACT

Paraneoplastic syndromes are tumour-associated, indirectly related clinical disorders. Here, we present a 58-year-old woman with impaired glucose tolerance and a gradual increase in white blood cell count. In May 2019, the patient was diagnosed with adenocarcinoma of the lung and engaged in a series of chemotherapy followed by PD-1 therapy at last. About a month following her last PD-1 cycle, she indicated some clinical disorders. Hematological studies on and after admission revealed a white blood cell count that progressively increased up to 84.69×109/L/L. CT scan of the abdomen unveiled the presence of a cyst and a tumour connected. Repeated blood cultures, as well as bacterial genetic testing of the cyst drainage, were all negative. Bone marrow biopsy exhibited a normal pathological appearance, and bone marrow liquid examination by flow cytometry was normal. Diagnosis of an adverse drug reaction of PD-1 therapy or a paraneoplastic syndrome was accepted. Following the patient's tumour progress, the patient was treated with a combination of Albumin paclitaxel and Endostar chemotherapy. After the treatment, a progressive restoration of the patient's condition, blood cell counts, and vital signs was observed. Three days after the treatment, the patient's platelet count significantly dropped, and she was given rhIL-11, which restored this number by day 8. The white blood cell count dropped on day 3 post-chemotherapy as well, but without any treatment, re-increased to 10.89×109/L on day 6 and more by day 7: 39.8×109/L, and up to 44.3×109/L by day 8.

Keywords: *Adenocarcinoma of the lung, Adverse drug reaction of PD-1, Paraneoplastic syndrome, Leukocytosis, Abnormal glucose tolerance.*

CASE REPORT

A 58-year-old non-smoking Chinese woman with a medical history of left lung cancer diagnosed 19 months earlier was presented for the second time on 27 January 2021 to The Third Affiliated Hospital of Kunming Medical University (Tumor Hospital of Yunnan Province), Kunming, Yunnan, China. Investigations on her first admission in May 2019 found degenerative, highly suspicious adenocarcinoma cells without EGFR mutation, the reason behind adenocarcinoma of the lung. A therapy with the combination of Pemetrexed and Cisplatin was started in June for a total of two cycles. In August 2020, her condition degenerated, and Bevacizumab was added to her therapy. Pemetrexed + Cisplatin + Bevacizumab was consumed for a total of two cycles. Finally, in October 2020, PD-1 therapy (once every two weeks) was started for a total of six times, the last time being in December 2020. Nearly a month after her last PD-1 therapy, abnormal glucose tolerance and a progressive increase in white blood cell count were recorded when she was admitted for the second time. Then, she was directed to the Cancer biotherapy Centre (Yunnan Cancer Hospital) for further treatment. Twenty days before this admission, she consulted elsewhere, where cytological examination found cancer cells in three

liters of bloody pleural effusion obtained from a closed thoracic effusion.

On admission, the patient was in a good mental state, with no weight loss, but presented a fever, which persisted throughout the hospitalization. The hematological studies of the patient resulted in 33.03×109/L white blood cell, 25g/L albumin, 73uMol/L creatinine, 128.21mg/L C-reactive protein (CRP) level, and 0.27ng/mL procalcitonin (PCT) level. These parameters quickly increased in the following days, like so: white blood cell 38.48×109/L, red blood cell 3.96×1012/L, hemoglobin in 119g/L, platelet 189×109/L, CRP 66.45mg/L, Albumin 26g/L, and creatinine 72 mmol/L. Repeated (three repeats) peripheral blood cultures were negative. Since admission, the patient was subjected to a large number of antibiotics, including antifungal and anti-inflammatory therapy, while the investigation was being done. Upon no bacterial identification, these treatments were terminated while other examinations continued. A computed tomography (CT) scan of the abdomen detected the presence of a cyst and a tumor connected in the left abdomen. However, the bacteriological study of a local puncture and drainage in the cyst was negative for bacterial and fungal detection. Bacterial genetic testing was negative as well. The white blood cells kept increasing up to 84.69×109/L/L. The patient's peripheral blood cell count was as follows: white blood cell 84.69×109/L, red blood cells4.04×1012/L, hemoglobin 120g/L, platelet 100×109/L/L. A bone marrow biopsy performed from the iliac bone revealed no tumor cell infiltration and a normal pathological appearance. Flow cytometry analysis of the bone marrow liquid found no signs of leukemia. An uncertain possibility of either an adverse drug reaction of PD-1 or a paraneoplastic syndrome was considered. Following investigations, it was noticed that the patient's cancer was progressing, indicating a probable PD-1 treatment failure. The patient was given chemotherapy with albumin paclitaxel and endostar-like Albumin Paclitaxel 200mg on Day 1, Day 8, and Endostar 210 mg in continuous pumping therapy from Day 1 to Day 6. After the chemotherapy, the patient's vital signs and peripheral blood cell count progressively became stable and normal.

Following the initiation of chemotherapy, the platelet number started decreasing to 57×109/L/L. Three days after chemotherapy, the patient's platelets were at their lowest number: 22×109/L; therefore, she was infused with platelets and was given recombinant human interleukin 11 (rhIL-11), which progressively restored platelet number to normal, with 51×109/L on day eight post-chemotherapy. However, three days after chemotherapy, the white blood cell count dropped to9.11×109/L and, without any specific treatment, started increasing daily to around the average value: 10.89×109/L on day 6. However, on day 7, these values suddenly increased to 39.8×109/L/L. On day eight, the white blood cell count was up to 44.3×109/L. The possibility of side effects of chemotherapy was considered. However, following the day eight checking and peripheral blood analysis results, our patient refused any advice or treatment and decided to be discharged from the hospital.

DISCUSSION

Paraneoplastic syndromes are clinical disorders that are associated with tumours but not directly caused by them.[1,2] Their prevalence, even less investigated in the literature, is estimated to be about 8% in cancer patients[3] and about 10% in lung cancer patients.[4] Frequently observed histologic subtype Adenocarcinoma causes a significant portion of lung cancers in many countries.[5] Within adenocarcinomas, particularly renal, pancreatic, and lung cancer, an uncommon type of paraneoplastic syndrome has been identified, known as hyperleukocytosis.[1] It is known that medication incorporating corticosteroids, the use of hematopoietic growth factors, infection, hematologic malignancy, as well as paraneoplastic syndrome can lead to the occurrence of leukocytosis.[6] Hyperleukocytosis is considered when the count of white blood cells is higher than 50×106/L to 100×106/L.[1] Our patient presented a progressive increase in white blood cell count that reached 84.69×109/L/L. The diagnosis in such patients with increased white blood cell count could be confused with acute leukemia.[1] However, unlike paraneoplastic hypercellularity, leukemia's present with immature myeloid cells.[1] Tumor infiltration in the bone marrow investigation was negative in the case of this patient. Blood cultures and microbial genetic tests were negative. Therefore, we excluded the possibility of microbial infection. Patients have also not been treated with hormones and cytokines during elevated white blood cells. Therefore, only adverse reactions of PD-1 paraneoplastic syndrome could be considered. Our non-smoking patient belongs to the small percentage estimated to be about 10%[7] of non-smoking patients diagnosed with lung cancer, and this condition is more frequent in women. Studies reported that the hematological manifestation of the paraneoplastic syndrome might be seen before or at the same time as cancer or even after the end of the cancer treatment, where it shows the disease recurrence or even during complete remission.[8,9] Our patient developed the condition about a month following her last cycle of PD-1 therapy. This may be a sign of the recurrence of her past disease since the CT scan of the abdomen found the tumor.

Adverse drug reaction of PD-1 consists of substantial toxic reactions following this therapy alone or in

association with chemotherapy or other targeted therapies.[10] In non-small cell lung cancer (NSCLC), research has indicated a greater occurrence of pneumonitis in patients who received PD-1 treatment compared to PD-L1 treatment.[11,12] Pneumonitis's most clinical symptoms include dyspnea, dry cough, chest pain, and fever.[13,14] Our patient presented only with a fever that persisted during her admission, and this could eventually be considered a symptom of PD-1 adverse drug reaction. A study showed that symptoms, including fever and increased white blood cell count, were observed with no bacterial or viral infection in NSCLC patients with immune-related encephalitis.[15] Our report exhibits similarities with this study. Our patient presented with an increasing white blood cell count that peaked at 84.69×109/L, a fever that persisted throughout her admission, with no bacterial or fungal infection. The administered treatment successfully restored the patient's vital signs and white blood cell count. However, she presented a decreased platelet count and an increased platelet count to normal after monitoring. This fluctuation was associated with a decrease in white blood cell count, followed by a spontaneous constant increase in white blood cell count. The decreased platelet count and the increased white blood cell count could be related to the side effects of the chemotherapy. However, it is important to consider the implications of an elevated white blood cell count on its own. Were those symptoms indicative of paraneoplastic syndrome or adverse drug reactions of PD-1?

CONCLUSION

We present a case of adenocarcinoma of a Lung patient who developed symptoms of paraneoplastic syndrome or adverse drug reaction of PD-1 after multiple cycles of chemotherapy following PD-1 therapy. The chemotherapy significantly improved the patient's condition; however, days later, she again entered into another cycle of clinical disorders. Intensive studies should be made to allow a better understanding of paraneoplastic syndrome or adverse drug reaction of PD-1 or any related condition for a better monitoring of such rare but existent cases.

SUGGESTIONS / RECOMMENDATIONS

For a better monitoring of lung adenocarcinoma, in-depth research is imperative to allow a better understanding of adverse drug reaction of PD-1 or paraneoplastic syndrome or any related condition.

CONFLICT OF INTEREST / DISCLOSURE

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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