



IL-6 and G-CSF production resulting from lung cancer in an HIV patient

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ABSTRACT

Increasing reports have noted an increased prevalence of lung cancer in human immunodeficiency virus (HIV)-positive patients with poor prognosis. A 51-year-old HIV-positive man was diagnosed with stage IV squamous cell lung cancer. He had high grade spike intermittent fever and persistent elevation of the white blood cell count as well as C-reactive protein (CRP) levels. Although we suspected opportunistic infections, we did not detect any infection. The autopsy showed positive immunostaining for Interleukin-6 (IL-6) in plasma cells of the stromal regions and G-CSF in tumor cells, which were considered responsible for his significant tumor fever, leukocytosis and high titers of CRP. This case report highlights the need to consider cytokine-producing tumor as a differential diagnosis of fever and high inflammatory status in HIV-positive cancer patients.

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Case illustrated

A 51-year-old human immunodeficiency virus (HIV)-positive man, a former smoker, who received anti-retroviral therapy (ART) presented to our clinic with fever and hemoptysis for two weeks. Chest computed tomography (CT) scan revealed a mass lesion and atelectasis of the right lung (Fig. 1). Consequently, he was diagnosed with stage IV squamous cell lung cancer (cT3N1M1c). He had high grade spike intermittent fever and persistent elevation of the white blood cell count as well as C-reactive protein (CRP) levels during the clinical course. Although we suspected opportunistic infections, we did not detect any infection during the intensive investigation including bronchoscopy. The patient's CD4 lymphocyte count had remained approximately 1,000/ μ L, and his

HIV-RNA had been undetectable. He had never experienced acquired immune deficiency syndrome (AIDS)-defining diseases and died 6 months after he was diagnosed with lung cancer. The autopsy showed positive immunostaining for Interleukin-6 (IL-6) in plasma cells of the stromal regions and G-CSF in tumor cells (Fig. 2), which was consistent with his laboratory findings (IL-6 1640 pg/mL, G-CSF 155 pg/mL).

Recently, increasing reports have noted an increased prevalence of lung cancer in HIV-positive patients with poor prognosis [1]. Also, G-CSF-producing cancers have been reported to be related to chemotherapy resistance and poor prognosis [2,3]. We usually consider opportunistic infections to be a cause of high fever and inflammatory status in HIV-positive patients. However, in this case, IL-6 production from stromal cells and G-CSF production from tumor cells were considered responsible for his significant tumor fever, leukocytosis and high titers of CRP. To the best of our knowledge, no studies showed inflammatory cytokines production resulting from AIDS-defining cancers in HIV patients by immunostaining. This case report highlights the need to consider cytokine-producing tumor as a differential diagnosis of fever and high inflammatory status in HIV-positive cancer patients.

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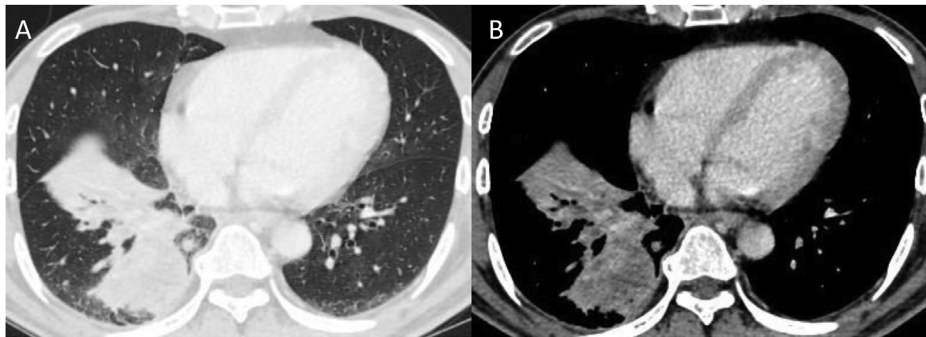


Fig. 1. Chest computed tomography at the time of referral showed tumor and atelectasis of the right lung (A: lung window, B: mediastinal window).

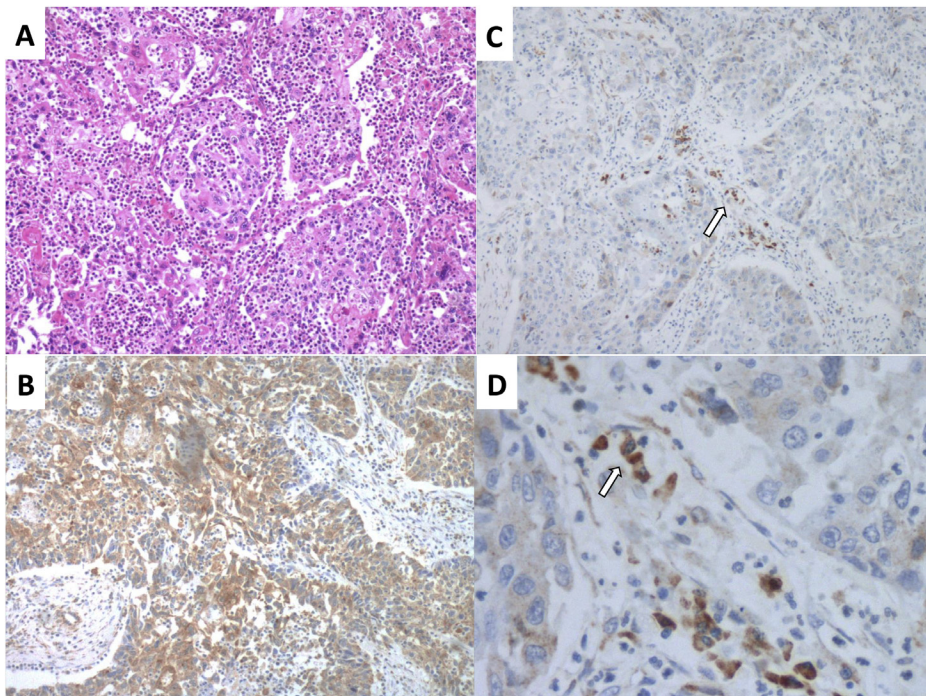


Fig. 2. A: Hematoxylin and Eosin staining of the lung cancer autopsy showing squamous cell carcinoma with high-grade dysplasia, B: Immunostaining for G-CSF showing positive findings for tumor cells. C (low magnification) and D (high magnification): Immunostaining for IL-6 showing positive findings for plasma cells (arrow) of the stromal regions.

Informed consent

Written informed consent was unobtainable because the patient is deceased.

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CRedit authorship contribution statement

Naoki Kawakami: Writing - original draft. **Ho Namkoong:** Conceptualization, Data curation, Project administration, Supervision, Writing - original draft, Writing - review & editing. **Katsunori Masaki:** Data curation, Writing - review & editing. **Yutaka Kurebayashi:** Data curation, Writing - review & editing. **Masayuki Shimoda:** Data curation, Writing - review & editing. **Hiroshi Kotani:** Data curation, Writing - review & editing. **Hiroshi**

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Declaration of Competing Interest

The authors have declared that no competing interests exist.

References

- [1] Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *Lancet HIV* 2017;4:e495–504, doi:[http://dx.doi.org/10.1016/S2352-3018\(17\)30125-X](http://dx.doi.org/10.1016/S2352-3018(17)30125-X).
- [2] Kasuga I, Makino S, Kiyokawa H, Katoh H, Ebihara Y, Ohyashiki K. Tumor-related leukocytosis is linked with poor prognosis in patients with lung carcinoma. *Cancer* 2001;92:2399–405, doi:[http://dx.doi.org/10.1002/1097-0142\(20011101\)92:9<2399::AID-CNCR1588>3.0.CO;2-W](http://dx.doi.org/10.1002/1097-0142(20011101)92:9<2399::AID-CNCR1588>3.0.CO;2-W).
- [3] Kawano M, Mabuchi S, Matsumoto Y, Sasano T, Takahashi R, Kuroda H, et al. The significance of G-CSF expression and myeloid-derived suppressor cells in the chemoresistance of uterine cervical cancer. *Sci Rep* 2015;15(5):18217, doi:<http://dx.doi.org/10.1038/srep18217>.