Lethal aplastic anemia caused by dual immune checkpoint blockade in metastatic melanoma

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A 48-year-old woman receiving combined ipilimumab plus nivolumab treatment for metastatic melanoma in a clinical study (CheckMate 401) was admitted to the Karolinska University Hospital with fever, nose-bleeds, easy bruising and fatigue. She had received four courses with the combination treatment followed by five courses of nivolumab, the last course was given three days prior the admission. Absolute neutrophil count was <0.1 x10^9/L, platelet count <5 x10^9/L and hemoglobin level 115 g/L (suppl.FigS1). The peripheral blood smear showed pancytopenia with only scattered lymphocytes (Fig1A). The bone marrow biopsy and aspirate showed aplasia; approximately 10% cellularity with scattered lymphoid and few erythroid cells without signs of dysplasia. Granulopoiesis and megakaryocytes were completely missing. The majority of lymphoid cells were CD8-positive T-lymphocytes.

Focally, stromal edema was noted without signs of fibrosis (Fig1B). Daily treatment with prednisone (1 mg/kg), and granulocyte colony-stimulating factor (G-CSF) was initiated. In protective isolation, the patient received standard antibacterial, antifungal and antiviral treatment and after her second day of admission she had no signs of infections. She received antifibrinolytic treatment with tranexamic acid and repeated platelet transfusions. Since there were no signs of recovery in her pancytopenia, arrangements were made to initiate aplastic anemia treatment with anti-thymocyte globulin (ATG), which also has been used to treat ipilimumab-induced hepatitis[1, 2]. However, at the eleventh day of hospitalization she suffered a brain hemorrhage with a rapid fatal outcome. Postmortem examination revealed a large intracerebral hemorrhage but no signs of brain/leptomeningeal metastases or vascular disease, hence the hemorrhage most likely resulted from the persistent thrombocytopenia. Microscopic examination of the postmortem bone marrow showed aplasia without engagement of melanoma cells (Fig1C). Immunohistochemistry confirmed the predominance of CD8-positive T-lymphocytes in the postmortem bone marrow (not shown). Microscopic examination of liver metastases showed viable melanoma cells with CD3- and CD8 positive lymphoid cell infiltration localized mostly at the periphery of the lesions (Fig1D and suppl.FigS2).

Immune checkpoint blockade with PD-1 and CTLA-4 inhibitors have proven effective in the treatment of metastatic melanoma and also of several other tumors[3]. Combination therapy with PD-1 inhibitor nivolumab and CTLA-4 inhibitor ipilimumab further improves progression-free survival in patients with metastatic melanoma, however the combination therapy increases the risk of immune-related adverse events, in particular diarrhea/colitis, hepatitis, pruritus/rash and endocrine dysfunction[4]. To the authors' knowledge, this is the first reported case of aplastic anemia with a lethal outcome, induced by ipilimumab and nivolumab combination therapy. In the summary of product characteristics (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf), grade 3-4 anemia, neutropenia and thrombocytopenia were reported in 2.8%, 0.7% and 1.2% of patients treated with nivolumab plus ipilimumab (n=448). Furthermore, there have been reports of cases with checkpoint blockade induced cytopenias [4, 5]. Collectively, this indicates that in a small proportion of patients receiving these treatments, bone marrow suppression occurs, in some cases probably resulting from T-cell activation against early hematopoietic progenitors. Our case illustrates the importance of detecting low peripheral blood counts timely in patients on

checkpoint blockade treatments, and if necessary withhold treatment and initiate a multidisciplinary approach to diagnose and treat this complication.

Disclosures

J.L. is consultant advisor to Eisai, BMS, MSD, GSK, Kymab, Pfizer, Novartis, Roche/Genentech, Secarna, Pierre Fabre and EUSA Pharma and has received institutional research support from BMS, MSD, Novartis, Pfizer. P.A.A. has a consultant/advisory role for BMS, Roche/Genentech, MSD, Novartis, Array, Amgen, Merck Serono, Pierre Fabre and has received research funds from BMS, Roche-Genentech and Array. J.H. has participated in advisory boards for BMS, Merck, Novartis and Roche. RK has served on Advisory Boards for BMS and Merck, Conference Reporter for BMS, Speakers Panel for BMS and Merck. All remaining authors have declared no conflicts of interest.

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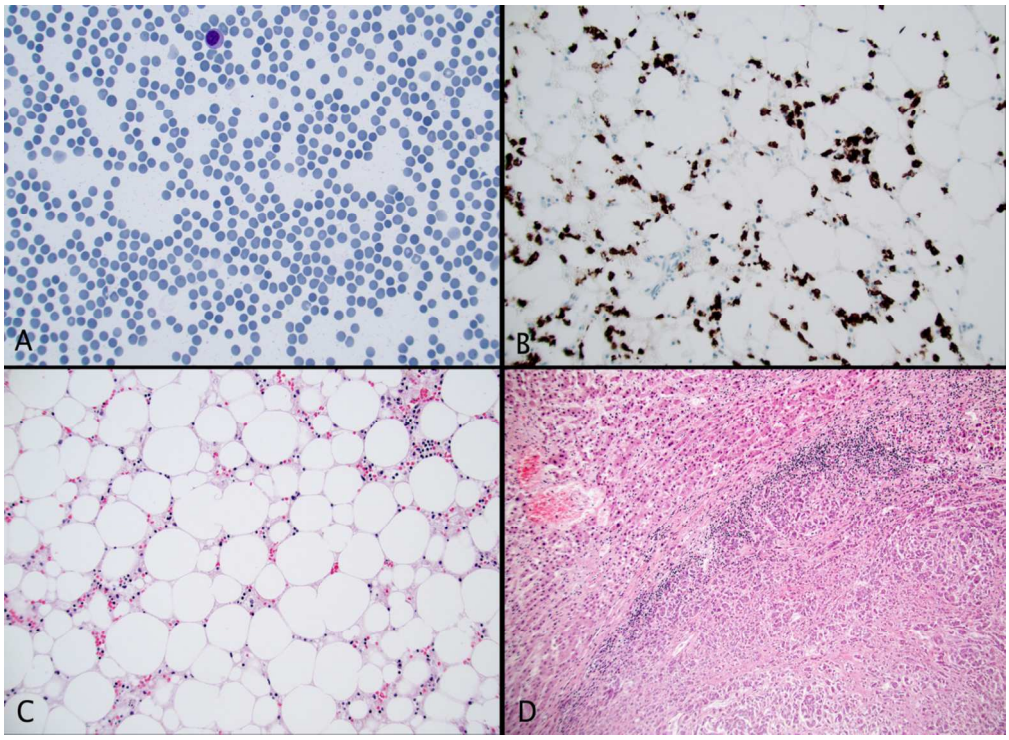
Figure 1. May-Grünwald-Giemsa-stained peripheral blood smear (40x magnification) showing pancytopenia with only scattered lymphocytes present (A). Immunohistochemical

stain for CD8 of the premortem bone marrow biopsy (20x magnification) with the majority of lymphoid cells CD8-positive (B). Hematoxylin and eosin stained section of the postmortem bone marrow (20x magnification) showing hypoplasia with scattered lymphoid and few erythroid cells without signs of dysplasia and granulopoiesis and megakaryocytes completely missing (C). Hematoxylin and eosin stained liver metastasis (20x magnification) showing viable melanoma cells with lymphocytes at the periphery of the lesions (A).

Supplementary Figure S1. The patient's peripheral blood cell counts and courses of treatment displayed in a timeline chart. The lower range of blood values are indicated by red asterisks on the y-axes.

Supplementary Figure S2. Hematoxylin and eosin stained liver metastasis (20x magnification) showing viable melanoma cells with lymphocytes at the periphery of the lesion (A). Same section of liver metastasis as in (A) with immunohistochemical stain for CD3, showing CD3 positive lymphoid cells infiltrating the periphery of the metastatic lesion (B).



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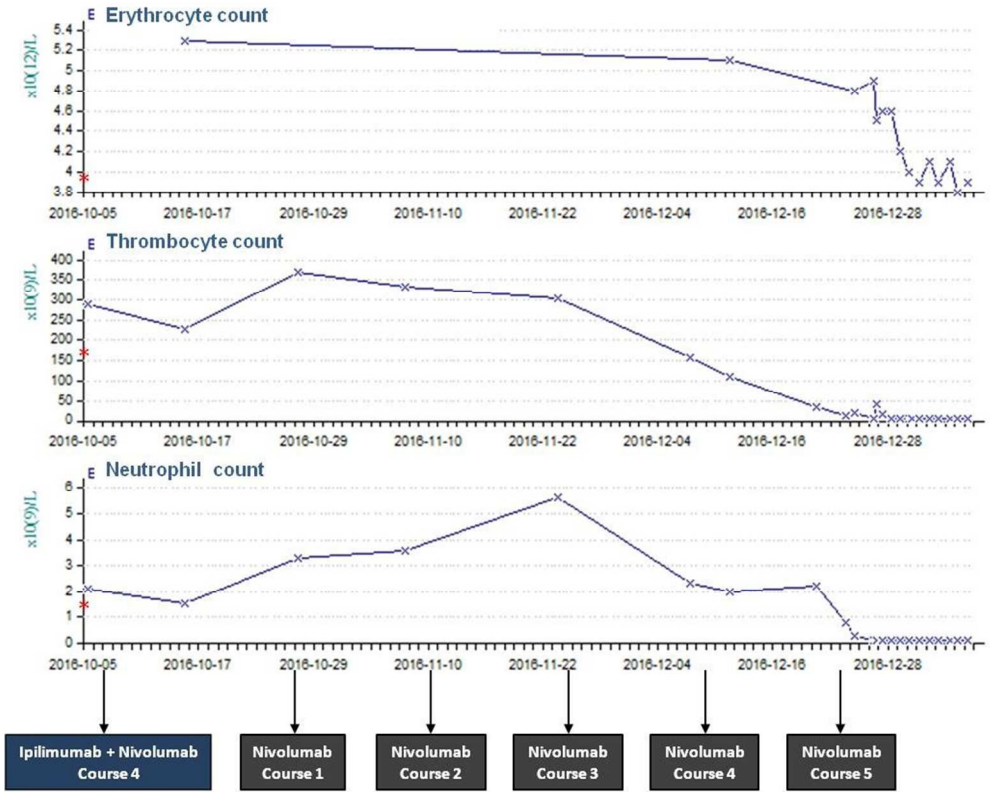

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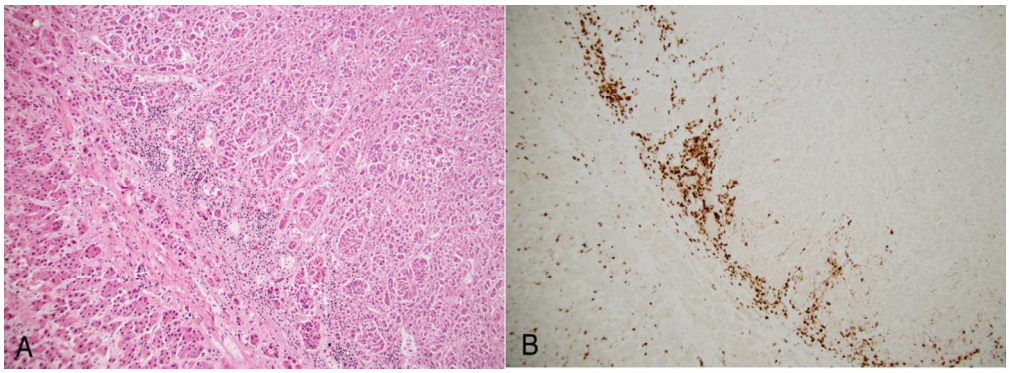

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