A Case of Immune Thrombocytopenia as a Rare Side Effect of an Immunotherapy with PD1-Blocking Agents for Metastatic Melanoma

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Introduction
Immune checkpoint blocking agents such as the CTLA-4 antibody ipilimumab or the PD1-antagonists pembrolizumab and nivolumab have been approved for the treatment of metastatic melanoma [1–4]. Ipilimumab blocks the CTLA-4 receptor on T cells and releases the breaks of the immune system by turning off inhibitory mechanisms in cytotoxic T cells. Pembrolizumab and nivolumab block binding of programmed death protein 1 receptor (PD1) on T cells and programmed death-ligand 1 (PDL1) on melanoma cells. Hence, due to the mode of action of these antibodies tumor-specific T-cell responses are restored. For ipilimumab as well as for both PD1 blockers, benefits in response rates as well as in progression-free and overall survival were proven in the past [1–4]. However, all of these drugs may induce autoimmune phenomena such as thyroid dysfunction, vitiligo, rash, autoimmune colitis, or pneumonitis [5, 6]. Cases of severe forms of autoimmune-mediated thrombocytopenia have been reported in singular cases only [7–10].

Case Report
We report the case of a 73-year-old male patient with a V600E BRAF-mutated metastatic melanoma. The malignancy had been revealed in March 2015 by axillary metastases of a malignant melanoma without known primary. After complete resection of all tumor masses, an adjuvant radiotherapy of axillary,
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Supra- and infraclavicular lymph nodes followed by an adjuvant immunotherapy with low-dose IFN-α was performed until December 2014. Under therapy with IFN-α Hashimoto thyreoiditis developed and was treated with orally administered thyroxin. In December 2014 disease progression occurred with disseminated lung, skin, lymph node, and bone metastases. The patient was first treated with the BRAF inhibitor LGX 818 within a clinical trial. Best response was regressive disease in April 2015, but due to disease progression (progressive disease in all metastatic sites) treatment had to be changed in December 2015. Platelet counts before and during this systemic therapy were slightly decreased with values around 130/nl (normal value 140–400/nl). To treat aching progressive bone metastases, a radiation of the left pelvis and hip was performed in December 2015 with a cumulative dose of 33 Gy. Then, a therapy with nivolumab (3 mg every 2 weeks) was started in the end of December 2015. Baseline blood tests were normal except of a mild thrombocytopenia (108/nl) that had been interpreted as a side effect of radiation. The first dose of nivolumab was well tolerated without any side effects. The application of the second dose led to an anaphylactic reaction presenting with generalized urticaria, hypotension, and tachycardia approximately half an hour after infusion completion. Therefore, in January 2016 treatment was changed to pembrolizumab with a dose of 2 mg/kg every 3 weeks after premedication with dexamethasone 8 mg, ranitidine 300 mg and clemastine 2 mg intravenously. Treatment was tolerated without any subjective side effects. In February 2016 therapy was stopped due to further disease progression with development of multiple brain metastases and worsened thrombocytopenia. Performing immune hematology testing in March 2016 using serum and platelets of the patient for the platelet immune fluorescent assay (PIFA) and the monoclonal antibody-specific immobilization of platelet antigen assay (MAIPA), free and cell-bound platelet-specific IgG autoantibodies could be detected [11, 12]. In detail, in two independent indirect PIFA assays on March 2 and 24, a relative fluorescence intensity of 43.8% and 48.0% was detected, respectively (cut-off >20%, negative controls 1.8% and 2.3%). The direct PIFA on March 24 proved that the patient’s platelets were strongly covered with IgG autoantibodies (relative fluorescence intensity 96.2%, cut-off >20%, negative control 13.8%). Moreover, performing the indirect MAIPA with the blood sample of March 2, neither alloantibodies against platelet-specific glycoproteins nor HLA-specific alloantibodies could be detected. Due to the clinical course and the laboratory results, it is likely that the thrombocytopenia is caused by an autoimmune-mediated genesis. However, other possible causes of thrombocytopenia were not excluded, e.g. by performing a bone marrow aspirate. Systemic corticosteroids were administered (first in a dose of 1 mg methylprednisolone/kg body weight, then tapered down). However, platelet counts returned to values around 130/nl not before July 2016. Figure 1 shows platelet count and therapy of autoimmune-mediated thrombocytopenia. Due to disease progression, a whole-brain radiation was performed with a cumulative dose of 36 Gy, followed by targeted therapy with dabrafenib and trametinib that led to a short-lasting partial response. The patient died due to metastatic disease in September 2016.

**Discussion**

Autoimmune thrombocytopenia can be classified into a primary or a secondary form, dependent on the absence or presence of associated or underlying diseases [13]. The secondary form may be associated with infections, e.g. HCV or HIV, malignant tumors, e.g. lymphoma or solid tumors, or with autoimmune diseases, e.g. Evans syndrome or lupus erythematoses [13]. Aboud and coworkers [13] could show in a large retrospective analysis that 11% of...
patients with autoimmune thrombocytopenia suffered from affec-
tions of the thyroid gland just as well as the patient presented here who
developed Hashimoto thyroiditis under therapy with IFN-α in the past. In
general, autoimmune disorders tend to co-exist in the same individual [14]. Boelaert et al. [15] could show that
patients with Hashimoto thyroiditis suffered from another
autoimmune disorder in 14.3%. The relative risk to develop an-
other autoimmune disorder such as pernicious anemia, systemic
lupus erythematoses, Addison’s disease, celiac disease, or vitiligo
was more than 10-fold elevated in patients with Hashimoto thyre-
oditis [15]. Whether the patient presented here suffered from au-
immune thrombocytopenia before treatment with checkpoint inhibitors
or not must remain speculative as laboratory testing was not per-
formed at that point in time. Though, a preexisting condition
seems to be most likely because platelet count was slightly de-
creased with values around 110/μl before immunotherapy with
PD1 blockers. In any case, therapy with nivolumab and pembroliz-
umab aggravated thrombopenia and induced or rather increased
the production of platelet-specific IgG autoantibodies. Due to this
case report and the laboratory results, it is likely that the thromb-
ocytopathy was caused by PD-1 inhibitor-induced platelet au-
toantibodies via an autoimmunity activation. However, other pos-
sible causes of thrombocytopenia were not excluded in this case.
Therefore, the final prove remains open.

To date, only a few cases of immune thrombocytopenia resulting
from therapy with checkpoint inhibitors have been published [7–
10]. However, in large prospective clinical trials investigating
checkpoint inhibitors in different malignancies, ‘cytopenia’ was re-
ported with an incidence between 5 and 17% [9]. Regrettably, the
genesis of thrombocytopenia has not been clarified in these studies.
Yet, it can be presumed that in a large part of cases with thrombocy-
topenia an autoimmune-mediated pathomechanism was causative.

In summary, the incidence of immune thrombocytopenia in tumor
patients treated with checkpoint inhibitors is potentially much
higher than previously suspected. Meticulous controls of blood
count are therefore essential. In cases of thrombocytopenia one should
bear in mind that low or declining platelet counts could be a sign of
immune thrombocytopenia.

Ethical Approval
Written informed consent from the patient was obtained.

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