Nivolumab and ipilimumab-induced eosinophilic granulomatosis with polyangiitis in a patient treated with dupilumab

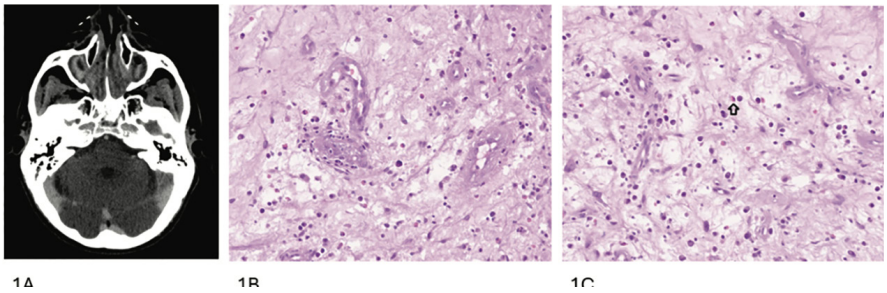

Fig. 1. Sinus computed tomography scan revealing massive maxillary and sphenoid chronic sinusitis with nasal polyps (Panel **A**). Histological examination of nasal biopsy showing vasculitis (Panel **B**) and inflammatory infiltrate with eosinophils (Panel **C**, arrow).

Sirs,

Following the introduction and growing use of immune checkpoint inhibitors (ICIs) in oncology, more robust evidence is emerging about the potential occurrence of immune-related adverse events, including vasculitis. On the other hand, dupilumab, a human monoclonal antibody that inhibits the signalling of both IL-4 and IL-13, is an effective therapeutic approach for both asthma and chronic rhinosinusitis with nasal polyps (CRSwNP), although some cases of drug-induced eosinophilia and anecdotal evidence of eosinophilic granulomatosis with polyangiitis (EGPA) occurring after dupilumab have been reported in the literature.

Here, we describe for the first time the occurrence of EGPA with severe peripheral nerve system involvement following the initiation of dual checkpoint blockade (ICB) with nivolumab and ipilimumab in a patient already treated with dupilumab for late-onset eosinophilic asthma and CRSwNP.

A 56-year-old man, who underwent removal of cutaneous melanoma in 2004, presented with a recurrence of neoplastic disease in October 2022 following the detection of pathological retroperitoneal lymphadenomegaly. His past medical history includes late-onset eosinophilic asthma (mean eosinophil count ranging between 600 and 900/μL), started at about 20 years of age, and CRSwNP requiring multiple surgical interventions and therapeutic courses with oral glucocorticoids, with only partial and transient clinical benefit. In March 2022, due to persistent and poorly controlled rhinosinusal disease, treatment with dupilumab, a human monoclonal binding the interleukin-4 receptor alpha subunit and inhibiting the signalling of both IL-4 and IL-13, was initiated after ear, nose and throat (ENT) evaluation. After 9 months, following the recurrence of melanoma, ICB with a combination of nivolumab (anti-PD1) and ipilimumab (anti-CTLA4) was started. Combination therapy was carried out for four cycles, followed by nivolumab alone. After four months from treatment initiation, the patient reported unintentional weight loss of 5 kg together with rapidly progressive stocking paraesthesia and hypoesthesia and severe motor deficit of the lower limbs with impaired dorsiflexion of the feet; therefore, after one month of nivolumab monotherapy, ICB was discontinued, treatment with prednisone 25 mg/day was started and the patient was admitted to the Neurology department. Here, a magnetic resonance imaging of the spine showed the presence of L4-L5 disc bulging resulting in a disco-radicular conflict, whereas nerve conduction studies revealed a severe lower limbs sensorimotor axonal polyneuropathy. In addition, during the hospital stay, the patient experienced worsening nasal obstruction and discharge, whilst blood tests revealed a slight increase of C-reactive protein (1.5 mg/dl) and a further elevation of peripheral eosinophil count up to 1500/μL despite treatment with glucocorticoids.

In the suspicion of EGPA, the patient was transferred to the Rheumatology department and steroid treatment was titrated up to prednisone 50 mg/day. Autoimmune panel, including ANA, ENA, dsDNA, rheumatoid factor and ANCA, was negative, whilst the negativity of stool cultures, coproparasitological examination, Trichinella, Toxocara, Strongyloides serology and full diagnostic workup for clonal hypereosinophilic syndrome allowed other causes of hypereosinophilia to be ruled out.

On whole-body computed tomography (CT) scan, signs of massive naso-ethmoidal polyposis and severe frontal, maxillary and sphenoid sinusitis was observed (Fig. 1A), in the absence of any evidence of active oncological disease or pulmonary ground glass opacities. During rhinoscopy a nasal polyp biopsy was performed, showing areas of necrosis and vasculitis with an eosinophil-rich inflammatory infiltrate (Fig. 1B/C). Echocardiography showed no kinetic defects, whilst serum B-type natriuretic peptide and Troponin I level were not increased. 24-h proteinuria was within normal range, whereas no signs of active glomerulopathy were present at microscopic examination of urine sediment. After multidisciplinary discussion with oncologists and neurologists, who ruled out an ICB-induced isolated peripheral neuropathy, a diagnosis of EGPA with severe PNS involvement was confirmed. Given the absence of clinical and radiological signs of active oncological disease, remission induction immunosuppressive treatment with rituximab (375 mg/m^2/week for 4 consecutive weeks), was started. After one month, the patient reported a significant improvement of neurological symptoms, with resolution of motor deficits, with only slight residual hypoesthesia on the soles of the feet, combined with normalisation of the eosinophil count and inflammatory markers. Oncological follow-up is continuing and the last whole-body CT scan performed at 12 months showed excellent response to immunotherapy

ICB is increasingly used for the treatment of various types of cancer; however, several cases of immune-related adverse events, including cases of vasculitis, have been reported in literature (1). Although numerous drug-induced disorders associated with eosinophilia have been described during treatment with nivolumab or ipilimumab (2-6), only two cases of EGPA, one induced by nivolumab (6) and one induced by ipilimumab (7) have been reported. To our knowledge, this the first description of EGPA following the initiation of dual ICB therapy in a patient treated with dupilumab. Although potentially effective on CRSwNP and asthma, the relationship between dupilumab and the development of vasculitis and/or eosinophilic manifestations in predisposed individuals is still controversial (8-9). A certain level of vigilance is recommended in patients with late-onset eosinophilic asthma and/or rhinosinusal disease treated with ICB, due to the potential development of organ-threatening manifestations due to EGPA.

Informed consent was obtained from the patient for the publication of this report.

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