Relapse of Birdshot Uveitis after Stopping Immunosuppressive Treatment and Starting Immune Checkpoint Inhibitors for Lung Cancer

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Abstract
A 56-year-old Caucasian woman with birdshot uveitis had to stop immunosuppressive treatment with adalimumab due to metastatic squamous lung carcinoma. She was subsequently treated with chemotherapy and pembrolizumab, an immune checkpoint inhibitor (ICI). After stopping adalimumab and starting pembrolizumab, the patient had an inflammatory relapse of birdshot uveitis with macular oedema. Birdshot uveitis is triggered by an unknown antigen presented on the HLA-A29 molecule which activates cytotoxic T-cells. Although immunosuppressive therapy effectively stabilizes birdshot uveitis, it might induce a higher risk of developing cancer. Treatment with ICIs, on the other hand, might exacerbate birdshot uveitis by increasing anti-tumoural immune reaction and inducing off-target autoimmunity.

Introduction
Birdshot uveitis (BU) is an uncommon, chronic, bilateral posterior uveitis typically affecting middle-aged white patients. Clinically, BU is characterized by primary stromal choroiditis and retinal vasculitis [1]. The exact pathophysiology of the disease is unclear, but
there is an important relationship to HLA-A29 and T-cell activation. Probably all BU patients harbour the HLA-A29 allele, and the presence of HLA-A29 is considered an essential criterion to diagnose BU [2]. BU is typically treated with chronic immunosuppressive treatment (IST), which can stabilize the disease in most cases [3].

**Case Presentation**

A 56-year-old Caucasian female was diagnosed with BU in 2013, at which time she noticed a reduction of visual acuity in the right eye. On presentation, best corrected visual acuity was 20/40 in the right eye and 20/25 in the left eye. Fluorescein angiography (FA) showed diffuse venous vasculitis and macular oedema in the right eye. Retinal imaging showed typical cream-coloured ovoid choroidal lesions, characteristic for BU. After excluding tuberculosis and sarcoidosis, BU was diagnosed, and this was confirmed by the presence of the HLA-A29 allele.

The patient was treated with methylprednisolone 64 mg/day, which was tapered over 3 months. The visual acuity improved to 20/20, and there was a resolution of the macular oedema. The patient was subsequently treated with azathioprine (Imuran®), but this had to be stopped due to mildly elevated liver enzymes and recurring macular oedema. The dose of prednisolone was increased again to 16 mg/day, and sirolimus (Rapamune®) was started. Initially, there was a good response with reduction of macular oedema; thus, prednisolone was tapered to 7.5 mg/day. However, after 4 months of disease stability, there was another relapse of macular oedema in the right eye. Therefore sirolimus was replaced by mycophenolate mofetil (CellCept®) in addition to prednisolone 15 mg/day. This change in therapy led to a slow and gradual reduction of macular oedema. After 24 months, the dose of prednisolone was reduced to 4 mg/day. Under this regime, the best corrected visual acuity remained 20/20 in both eyes for almost 2 years.

After these 2 years, there was a recurrence of macular oedema in both eyes, and therefore the therapy was switched to cyclosporine A (Neoral®) in combination with prednisolone 8 mg/day, under strict monitoring of the patient’s known arterial hypertension by the general practitioner. Despite good control of intra-ocular inflammation for 28 months in both eyes, cyclosporine A had to be substituted by the TNF-α blocker adalimumab (Humira®) subcutaneous injections every 2 weeks due to uncontrolled arterial hypertension. Again, there was an excellent treatment response, and we were able to slowly taper prednisolone over a 24-month period. Meanwhile the patient’s visual acuity remained stable, and OCT showed no macular oedema bilaterally. On FA, there was clear improvement of retinal vasculitis with adalimumab, but indocyanine green angiography revealed no effect on choroidal vasculitis, leaving very extensive hypocyanescent dark dots in both eyes. Adalimumab monotherapy was continued for another 12 months.

In April 2021, the patient was diagnosed with metastatic squamous non-small-cell lung carcinoma of the left lower lobe with involvement of bone, liver, and pleura. Therefore, adalimumab was stopped immediately. The different immunosuppressive drugs that were used in this case are shown in Table 1.

The patient was treated by the oncologists in May 2021 with combined chemo- and immunotherapy (carboplatin-paclitaxel-pembrolizumab). In August 2021, she was put on a maintenance therapy with pembrolizumab which led to an improvement of her general condition (less pain and a reduction of tumour size on chest CT). At that time, she also received radiotherapy (1 × 8 Gy) of the lower spine for bone metastasis. However, in December 2021, we documented an increase in cystoid macula oedema as shown in Figure 1.
Table 1. Summary of immunosuppressive medications used to control BU in our patient

| Immunosuppressants   | Dose                        | Duration of treatment                                      | Causes of drug termination                                                                 |
|----------------------|-----------------------------|------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Azathioprine         | 150 mg/day                  | 4 months in combination with prednisolone tapering scheme  | No reduction of macular oedema and mildly elevated liver enzymes                          |
| Sirolimus            | 2 mg/day                    | 4 months in combination with prednisolone tapering scheme  | Relapse in the macula oedema in the right eye                                            |
| Mycophenolate mofetil| 2 g/day                     | 24 months in combination with prednisolone tapering scheme| Recurrent macular oedema in both eyes                                                    |
| Cyclosporine A       | 200 mg/day                  | 28 months in combination with prednisolone tapering scheme | Uncontrolled arterial hypertension and impaired renal function                           |
| Adalimumab           | 80 mg at week 0, then 40 mg at week 1, then 40 mg every 2 weeks | 24 months in combination with prednisolone tapering scheme and 12 months as monotherapy | Diagnosis of metastatic spinocellular lung carcinoma                                      |
Discussion

BU is a rare auto-immune uveitis with an incidence of 0.2–1.7 cases per 100,000 [4]. There is a strong association with the HLA-A29 allele, which suggests its role in the pathogenesis of BU [5]. HLA-A29 is a class I major histocompatibility complex which can bind different antigens. In the antigen-presenting cell, an unknown peptide is processed intracellularly and expressed on the surface of the HLA-A29 molecule. This antigen binds to a T-cell receptor, leading to activation of the cytotoxic T-cell [6]. The exact antigen that triggers autoimmune in BU is not known. There are many microbial and viral antigens that share structural similarities to retinal antigens that may induce retinal autoimmunity [4, 6]. However, the causative antigen might also be an oncogenic peptide. Although the evidence is circumstantial, there is a hypothesis that BU might result from an effective anti-tumoural immune response to a subclinical melanoma or other tumour, with off-target cross-reactive autoimmunity. According to this theory, the immune response is able to destroy the tumoural cells but might lead to a cross-reaction against melanocytes in the choroid, leading to BU [7].

BU is a chronic T-cell mediated disease, which is treated with immunosuppressive drugs. Although chronic IST seems effective to stabilize the disease and to preserve visual function, it might be associated with an increased risk of developing infections and cancer [8, 9].

Fig. 1. a, b represent FA and ICGA of the right and left eye, respectively, during treatment with cyclosporine a: note the venous vasculitis and macular oedema at FA and hypocyanescent dark dots on ICGA. c, d represent FA and ICGA of the right and left eye, respectively, during treatment with adalimumab: note the effect of the latter on vasculitis but not on choroiditis. e, f represent FA and ICGA of the right and left eye, respectively, once adalimumab was stopped and after initiation of pembrolizumab: note the increase in cystoid macular oedema. ICGA, indocyanine green.
In this case report, the patient was treated by several immunosuppressive drugs (Table 1), with varying efficacy. Eventually, the retinal disease and macular oedema was controlled by monotherapy with adalimumab. Unfortunately, the patient, who was a smoker, developed a squamous non-small-cell lung cancer (NSCLC), and adalimumab was stopped.

Recently, immune checkpoint inhibitors (ICIs) have revolutionized treatment of certain types of cancer, such as squamous NSCLC. In patients with previously untreated metastatic, squamous NSCLC, the addition of ICIs to chemotherapy resulted in significantly longer overall survival and progression-free survival than chemotherapy alone [10].

In contrast to immunosuppressive drugs, ICIs enhance the anti-tumoural immune response by inhibiting immune checkpoints and thereby release the brakes on T-cells. Although this treatment is a major breakthrough in oncology, it can be associated with a lot of immune-related adverse events, including eye problems, such as uveitis [11].

In this case, the patient was treated with chemotherapy and pembrolizumab, a humanized IgG4 monoclonal antibody selective for programmed cell death protein 1 (PD-1). Recently, Acaba-Berrocal et al. [12] reported a case of birdshot-like uveitis in a HLA-A29-negative patient treated with pembrolizumab for metastatic cutaneous melanoma. This interesting case suggests that unleashing the anti-tumoural immune reaction by ICIs mimics BU, even in the absence of HLA-A29. This might support the theory that BU is the result of melanoma/tumour immune surveillance with cross-reactive anti-melanocytic auto-immunity in the eye and might explain why BU is almost exclusively found in middle-aged whites, as they are more prone to developing melanoma [13].

In our case report, there was an increase in macular oedema and retinal vasculitis on FA after stopping adalimumab and starting pembrolizumab. It is difficult to determine whether the disease relapsed due to stopping adalimumab or due to starting pembrolizumab or a combination of both. It is also impossible to determine whether there was already a subclinical tumour before the diagnosis of uveitis in this smoking patient.

Further research is warranted to unravel the exact pathophysiology and the possible role of an oncogene in BU. If the oncological hypothesis is true, this would mean that BU patients that are treated with IST are more vulnerable to developing cancer. But regardless of this theory, this case reminds us that chronic IST can be associated with a higher risk of developing cancer.

**Conclusion**

T-cells have a conflicting role in BU and tumour immunity. On the one hand, BU is a T-cell-mediated auto-immune disease that can be treated with immunosuppression and more specifically T-cell suppression. On the other hand, T-cells have an important function in tumour surveillance, which can be compromised when T-cells are suppressed. This case reminds us to be vigilant for the development of cancer in BU patients, especially when they are treated with chronic IST.

**Statement of Ethics**

This study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mohammed Alsaddi and Pieter-Paul Schauwvlieghe were the only contributors to the drafting of the manuscript including literature search, data collection, data analysis, and data interpretation. Kathy Hondeghem helped with medical editing. The authors reviewed and approved the final manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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