Brentuximab vedotin induced uveitis

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ABSTRACT

Purpose: To report a case of bilateral Vogt-Koyanagi-Harada (VKH)-like granulomatous pan uveitis secondary to brentuximab vedotin (BV) administration to treat for classical Hodgkin lymphoma (CHL).

Observations: A case of bilateral pan uveitis is described, following administration of BV, with features of VKH-like uveitis: presence of inflammatory cells in the anterior and posterior segment, multiple small serous detachments around the optic disc and retinal pigment epithelium (RPE) folds confirmed by optical coherence tomography (OCT) as well as hypocyanescent dark dots, disc hyperfluorescence and fuzzy vascular patterns seen on indocyanine green and fluorescein angiography. There were no systemic features of VKH disease. Further etiological investigation showed no clear infectious or inflammatory cause. The uveitis responded well to treatment with corticosteroids and cessation of BV. A relapse occurred a few months later when BV treatment was reinitiated, suggesting a probable adverse event to this drug, according to the Naranjo algorithm.

Conclusions: We hypothesize that administration of BV can induce a VKH-like uveitis, caused by loss of function of protective CD30+ cells present in the uveal tract, possibly aggravated by collateral damage to surrounding CD30+ cells and melanocytes, leading to a uveal immune reaction. It is therefore important for the clinicians using BV to be aware of this adverse event. Growing experience with immunotherapy will provide more clinical insights in these complex immune mechanisms in the future.

1. Introduction

Targeted cancer therapies have become an interesting alternative to treat various types of oncological pathologies. Despite their undisputed efficacy, these treatments can be complicated with immune-related adverse events and cause autoimmune reactions including systemic and organ-specific autoimmune reactions like uveitis.1

Brentuximab vedotin (BV) is a CD30-directed antibody-drug conjugate, consisting of an anti-CD30 monoclonal antibody and an antimitotic agent monomethylauristatin E (MMAE). It delivers an antineoplastic agent resulting in selective apoptotic cell death in CD30 expressing tumour cells. CD30 is a tumour necrosis factor receptor expressed in activated B- and T-cells, as well as Reed-Sternberg cells, typical for Hodgkin lymphoma, and Hallmark cells, present in anaplastic large cell lymphoma. After internalization of the antibody-drug conjugate-CD30 complex, MMAE is released within the cell. Binding of MMAE to tubulin disrupts the microtubule network within the cell inducing cell cycle arrest and resulting in apoptotic death of the CD30 expressing tumour cell.2

BV is approved for the treatment of adult patients with relapsed or refractory CD30 positive Hodgkin lymphoma or systemic anaplastic large cell lymphoma. Multiple studies show efficacy with clinically relevant results, improving the prognosis of this refractory disease, with an acceptable safety profile.3

2. Case presentation

A 71-year-old Caucasian female with a history of relapsed classical Hodgkin lymphoma (CHL), stage IIb, treated with BV, was referred to our ophthalmological department in Antwerp with blurry vision. She was diagnosed with CHL two years earlier and initially reached remission after two cycles of chemotherapy ABVD (Adriamycin (doxorubicin), Bleomoxane (bleomycin), Velban (vinblastine), DTC (dacarbazine) – all given as a venous infusion on days 1 and 15). One year later, after four

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cycles of this chemotherapy and adjuvant radiotherapy to the spleen, she developed an abdominal lymph node recurrence. Because of the progression, a second line chemotherapy, carboplatin/gemcitabine, was started with poor haematological tolerance and little effect. After a few months, the patient received BV. Three weeks after the first administration, she developed visual loss and floaters in both eyes, slight photophobia but no pain.

At presentation, visual acuity was 20/40 in both eyes. Slit lamp evaluation with fundoscopy showed granulomatous pan uveitis: anterior chamber cells right eye 2+ and left eye 1+ (Standardization of Uveitis Nomenclature⁴), granulomatous endothelial precipitates, poor pupil dilation with phenylephrine 2.5% and tropicamide 0.5%, but no posterior synechiae. The view of the fundus was obscured by vitreal haze 2+. There were no signs of retinal infiltrates, exudates or haemorrhages, but there were multiple small serous detachments around the optic disk in both eyes. Intra-ocular pressure was within normal limits.

Optical coherence tomography (OCT) of the left eye showed retinal pigment epithelium (RPE) folds, moderately thickened choroid and peripapillary subretinal fluid. The right eye had a normal foveal depression with a moderately thickened choroid and a limited amount of peripapillary subretinal fluid (Fig. 1).

The clinical image was suggestive of Vogt-Koyanagi-Harada (VKH)-like pan uveitis. There were no extra-ocular symptoms or associated systemic findings such as headache, tinnitus, or vitiligo. There were no arguments for an infectious cause. Moreover, before starting BV treatment, serological testing for infectious diseases (including tuberculosis) was performed and was negative. Serial PET-CT scans did not show any pulmonary granulomatous lesions, which would have been suggestive for sarcoidosis or tuberculosis. Therefore, we concluded that the uveitis was possibly linked to the administration of BV and was possibly an immune-related adverse event. The patient was started on oral steroid therapy (methylprednisolone 64 mg per day with slow tapering over 3 months), initially without interruption of the targeted chemotherapy.

At follow-up visit one week later, visual acuity was 20/32 in both eyes. There was a slight reduction in anterior chamber inflammation in both eyes, less subretinal fluid in the left eye and a decrease in choroidal thickness in both eyes on OCT-imaging. Fluorescein angiography (FA) was performed which showed dense floaters, no obvious vascular leakage or vasculitis and slight optic disk leakage (Fig. 2). On indocyanine green angiography (ICGA), visualisation of the posterior pole was hindered by the central floaters, but there were some hypocyanescent spots centrally and peripherally in both eyes, suggestive of disappearing choroidal granulomas. We presume the image would have been more evident had we performed ICGA a week earlier, since active granulomas can disappear under corticosteroid therapy, which was already initiated at the time.⁵

In agreement with the treating haematologist, BV admission was interrupted. Oral corticosteroids were continued, and topical corticosteroids were associated (prednisolone acetate 3 times daily). One week later anterior chamber inflammation decreased with only sporadic cells in both eyes. OCT imaging showed resolution of subretinal fluid. Because of persisting visual acuity loss caused by disturbing dense vitreous floaters and the presence of cataract, both eyes underwent combined phacoemulsification with lens implant and pars plana vitrectomy with vitreous sampling and subsequent histopathological investigation of the vitreous. No light or heavy immunoglobulin chain alterations were found, and cytology was not suggestive of lymphoma. Methylprednisolone was tapered and stopped in the 14th week following the first visit.

One month after vitrectomy, left and right eye respectively, the...
anterior chamber and posterior segment remained clear with no significant flare and visual acuity was stable.

BV was reinitiated a few weeks later causing an immediate recurrence of uveitis with increased anterior chamber flare and cells, and cellular reaction in the vitrectomized posterior cavity. BV was stopped again because of the uveitis and the patient had started complaining of disturbing peripheral neuropathy. Topical corticoid therapy (prednisolone acetate 3 times daily, tapering each week) were started and after one month the ocular symptoms improved and the eye was quiescent on slit lamp evaluation.

3. Discussion

To the best of our knowledge, this is the first case of bilateral granulomatous pan uveitis related to BV administration. One case of BV related bilateral Purtscher-like retinopathy has been described, as well as a case series (three cases) of cytomegalovirus retinitis. Other, non-ocular, side effects are described in literature such as peripheral neuropathy, progressive multifocal leukoencephalopathy, and pancreatitis.

Our case shows a VKH-like pan uveitis with vitritis, multifocal choroidal thickening and undulating aspect of the retinal pigment epithelium, multifocal subretinal fluid collections and mild granulomatous anterior chamber reaction, but no systemic changes (vitiligo, depigmented eyelashes/eyebrow, meningismus).

BV is a chimeric monoclonal antibody targeting CD30, coupled to MMAE, an antimitotic agent inhibiting tubulin formation and resulting in tumour cell apoptosis. CD30 is part of the tumour necrosis factor
superfamily with pleiotropic function and can be found on a small subset of activated B- and T-cells present in a variety of lymphoid neoplasms, most classical in Hodgkin lymphoma and anaplastic large cell lymphoma. It is not present in naive and resting B- and T-cells. \(^{2,3}\) BV binds to the CD30 receptor which is followed by receptor endocytosis and cleavage of the antiapoptotic agent by intracellular lysosomes.\(^{3,4}\) This leads to apoptosis of the tumour cells and other CD30 positive cells. Surrounding cells can be damaged by the released antiapoptotic agent causing bystander effects.\(^{5,6}\) The tumour cells can also release CD30 positive extracellular vesicles, which can bind to CD30 ligand expressing cells elsewhere in the body.\(^{7}\) In this way, they present additional membrane-associated CD30 binding sites and cause BV cellular toxicity to non-tumour cells.\(^{8}\) It is also demonstrated in tumour models and patients with Hodgkin lymphoma that MMAE promotes antigen presentation with enhanced dendritic cell maturation and T-cell proliferation.\(^{1}\)

Interestingly, elevated levels of soluble CD30 (sCD30) have been detected in aqueous humour samples from patients with granulomatous autoimmune uveitis, typically in VKH disease.\(^{12}\) The role of CD30+ cells in uveitis is still unclear. Possibly these cells have a protective function. CD30 is a positive regulator of apoptosis and has been shown to limit the proliferative potential of autoreactive CD8 effector T cells and protect the body against autoimmunity. An elevated level of sCD30 might reflect apoptosis and proteolytic cleavage of these protective CD30 cells, leading to more autoimmunity and proliferation of autoreactive effector T cells.\(^{13}\)

In light of these findings, we hypothesize that the clinical image of VKH-like uveitis in our patient could be caused by two separate mechanisms, probably enhancing each other.

The first mechanism would consist of a direct cytotoxic effect on a small amount of CD30 positive T cells present in the uveal tissue, with loss of the protective function of these CD30 cells, leading to more autoimmune T cell mediated inflammation, probably guided against melanocytes in the uvea, as is the case in classic VKH disease. As a second mechanism of enhanced autoimmunity, we propose bystander killing of non-lymphoma cells by the antiapoptotic agent MMAE with subsequent antigen presentation and T-cell mediated reaction, leading to a complex immune cascade.

The function of CD30 and CD30 ligands is complex and not completely understood. It plays a major role in cell proliferation and apoptosis.\(^{5,14}\) The very low level of CD30 expression present in normal ocular tissue, as measured by Abu El-Arser et al.,\(^{12}\) might explain the rarity of VKH-like uveitis in our patient, as well as its relatively mild form, with only moderately thickened choroid and limited amount of subretinal fluid, compared to true VKH disease. A potential role of unintended targeting of low-level pancreatic CD30 positive cells has also been suggested as a possible cause for the rare complication of pancreatitis after administration of BV.\(^{15}\)

To rule out the possibility that the uveitis was a manifestation of secondary ocular lymphoma itself, only a chorioretinal biopsy could be conclusive, which is a very invasive procedure to perform in an eye with a good visual prognosis. In our opinion though, secondary ocular lymphoma is rather unlikely in this case. The typical clinical aspects of haematogenous spread from a systemic lymphoma are different. They mostly appear in the uveal tract through the choroidal vascularization.\(^{16,17}\) A secondary ocular lymphoma very rarely presents with neurosensory retinal involvement or anterior chamber disease or iritis and only rarely affects the vitreous.\(^{16,18}\) CHL metastasis to the choroid and the retina is extremely rare and generally presents with an overall clinical appearance similar to hypertensive retinopathy, not present in our patient.\(^{16}\)

Since chorioretinal biopsy was too invasive, a biopsy of the vitreous with histopathological investigation was performed to investigate for ocular lymphoma.\(^{17}\) Vitreous samples from both eyes showed no light or heavy immunoglobulin chain mutations and no aberrant lymphocytes on cytology. However, we must note that at the time of the vitreous samples, the patient was treated with systemic steroids, which can mask the presence of lymphoma.\(^{19}\) Nevertheless, clinical evolution makes its possibility rather unlikely. After steroids were tapered, the patient remained symptom-free until she was re-challenged with BV. After ceasing BV therapy for a second time and only with mild topical steroids, the ocular inflammation resolved again, suggesting a reaction to BV rather than an ocular lymphoma which would probably resurface after ceasing the steroids. When calculating the Naranjo-score (\(>9 = \text{highly probable, } 5–8 = \text{probable, } 1–4 = \text{possible and } <0 = \text{doubtful}\) for VKH-like uveitis caused by BV, the score of 5, or 8 if we consider lymphoma ruled out, indicates a probable causative reaction (Table 1).\(^{20}\)

### 4. Conclusion

In conclusion, we report a case of a VKH-like pan uveitis, probably secondary to a recently introduced targeted salvage therapy, brentuximab vedotin, in a patient with relapsed and refractory classical Hodgkin Lymphoma. There was a good response to corticosteroids and cessation of brentuximab vedotin, but the uveitis recurred on rechallenge with brentuximab vedotin. We hypothesize that the uveitis is caused by a direct effect on CD30+ cells in the uveal tissue, with loss of their protective immune regulating function and/or by bystander cytotoxic effects of the antiapoptotic conjugate drug MMAE to surrounding non-lymphoma cells. Growing experience with immunotherapy will provide more (clinical) insight into these complex immune mechanisms in the future.

### Patient consent

The patient consented in writing for her case to be published.

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### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

### Table 1

| Question | Yes | No | Don’t know | Score |
|----------|-----|----|------------|-------|
| 1 | Are there previous conclusive reports on this reaction? | +1 | 0 | 0 | 0 |
| 2 | Did the adverse event appear after the suspected drug was administered? | +2 | –1 | 0 | +2 |
| 3 | Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered? | +1 | 0 | 0 | +1 |
| 4 | Did the adverse reaction reappear when the drug was readministered? | +2 | –1 | 0 | +2 |
| 5 | Are there alternative causes (other than the drug) that could on their own have caused the reaction? | –1 | +2 | 0 | –1/ +2 |
| 6 | Did the reaction reappear when a placebo was given? | –1 | +1 | 0 | 0 |
| 7 | Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 | 0 |
| 8 | Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | +1 | 0 | 0 | 0 |
| 9 | Did the patient have a similar reaction to the same or similar drug in any previous exposure? | +1 | 0 | 0 | 0 |
| 10 | Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 | 1 |
Declaration of competing interest

The following authors have no financial disclosures: (insert initials of the authors who have nothing to disclose: ST, MS, JJ, PPS.

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