Bilateral Panuveitis and Exudative Retinal Detachments Associated with Alpelisib

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Abstract
We report a case of alpelisib-induced uveitis. A 68-year-old female who had recently been given alpelisib for metastatic breast cancer presented with a 2-week history of bilateral worsening vision with a corresponding acute hypermetropic shift. Her unaided visual acuity was 6/60 in both eyes, with bilateral anterior uveitis, non-granulomatous keratic precipitates, posterior synechiae, and limited fundal view. There was also a mild iris bombe configuration, although the intraocular pressures were normal. Ocular ultrasound revealed bilateral uveal effusion, ciliary body congestion, dense vitreous cells, and exudative retinal detachments. These findings were also confirmed on multimodal imaging with widefield fundus photography (Optos) and optical coherence tomography. Based on the clinical features above, a diagnosis of alpelisib-induced panuveitis was diagnosed. She was then admitted and treated with a 3-day course of intravenous methylprednisolone and intensive topical steroids. Her clinical signs and symptoms started to improve, and she was discharged 4 days later. At 1 week of follow-up, her best-corrected visual acuity was 6/12 in both eyes, with broken posterior synechiae and resolution of exudative retinal detachments. This case highlights the importance of early ophthalmology involvement by the oncology team as oncology therapy can have potential unexpected ocular manifestations.
Introduction

Over recent years, immune-based therapies for breast cancer have been becoming more popular, with multiple clinical trials yielding promising results [1, 2]. One of these new immunotherapies is alpelisib (Piqray™), a phosphatidylinositol 3-kinase (PI3K) inhibitor developed by Novartis with specific activity against PI3Kα. It is used in combination with fulvestrant to treat hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced or metastatic breast cancer with a PIK3CA mutation in both women and men [3]. The main adverse effects of alpelisib reported in the initial clinical trials included hyperglycaemia, rash, and diarrhoea [4]. To our knowledge, this is the first reported case of alpelisib-induced uveitis.

Case Presentation

A 68-year-old Caucasian female was referred urgently to our tertiary uveitis unit with a 2-week history of bilateral hazy vision, which had worsened over the previous 3 days. Her presenting complaint was described as a “mesh across her vision,” although she denied symptoms of flashing lights and floaters. This was accompanied by a concomitant itchy rash in both her legs. Her past medical history included stage IV bilateral breast cancer, which had been treated with mastectomy, chemotherapy, and radiotherapy 12 years previously. However, only recently she was found to have metastases to her sternum and lung. For this indication, she was started on targeted therapy of alpelisib 300 mg once daily, also known as Piqray (BYL719). Unfortunately, this had to be temporarily stopped after 3 months due to diarrhoea. An attempt to restart alpelisib was again unsuccessful with the diarrhoea recurring 2 weeks after it was restarted. It thus had to be stopped, a stool sample was taken, and she was subsequently started on co-amoxiclav 625 mg three times a day and loperamide 2 mg when required after loose stools (maximum 16 mg per day) for presumed gastroenteritis. The rest of her past medical history was unremarkable. At the time of presentation, she had been on co-amoxiclav for 6 days, whilst all of her other medication had been stopped by her oncologist until her diarrhoea was under control.

Her past ophthalmic history was hypermetropia, with a recent attendance 1 week prior to presentation to her optician for updated refraction. A hypermetropic shift was noted in comparison to her previous refraction 9 months previously, with her prescription increasing from +3D to +6.75D on the right and +3.25D to +4.75D on the left.

On examination, her unaided visual acuity was 6/60 in both eyes. Clinical findings included bilateral anterior uveitis with 2+ cells and non-granulomatous keratic precipitates in the Arlt’s triangle. Both anterior chambers were shallow with a mild iris bombe configuration secondary to 360° posterior synechiae, as seen in Figure 1. However, intraocular pressures in both eyes were within the normal range at 11 mm Hg. The fundal examination was limited due to bilateral vitreous cells and haze.

Ocular ultrasound was performed which revealed bilateral shallow anterior chambers, shortened axial lengths, dense vitreous cells, exudative retinal detachments, and choroidal thickening extending from the ciliary bodies. Further multimodal imaging was performed with widefield fundus photography (Optos) showing the retinal detachments, as shown in Figure 2a, and optical coherence tomography demonstrating choroidal thickening. The hypermetropic shift was therefore explained by the exudative retinal detachments and shortened axial lengths.

A diagnosis of alpelisib-induced panuveitis was made based on these clinical findings. She was admitted to the tertiary eye hospital for a 3-day course of intravenous methylprednisolone (1 g). She was also started on hourly steroid eye drops and topical cyclopentolate 1% three times a day.
times a day to both eyes and given 1 mL subconjunctival dexamethasone (3.3 mg in 1 mL) and 0.3 mL subconjunctival mydricaine number 2. All of her parameters were stable on admission, and a wide range of blood tests was taken. An autoimmune screen (including ANCA, ACE, ANA, C3, C4, ENA, IgG, IgA, IgM, and RF) was taken and was within normal limits except for a mildly raised complement 3 (2.12 g/L). The rest of the blood tests (including FBC, CRP, LFT, U&E, HBA1C, calcium, and random glucose) were within normal limits apart from a raised white cell count (18.3 × 10^9/L), a raised C-reactive protein (183 mg/L), and a raised erythrocyte sedimentation rate (101 mm/h). A TB IGRA assay (QuantiFERON) was also negative, and her chest X-ray was normal with no evidence of tuberculosis.
During the course of her initial treatment, there was reversal of her white cell count elevation, with resolution of the “mesh effect” across her vision. On day two of admission, she was noted to be hypotonous with an IOP of 2 mm Hg on the right and 4 mm Hg on the left, which slowly improved. Blood cultures were taken, which were also unremarkable. When her short course of intravenous steroids ran its course, she was started on high-dose oral prednisolone (60 mg) and a topical steroid taper was started (initially decreased to six times a day). She continued to improve as the posterior synechiae started to break and the iris bombe resolved. Her diarrhoea also resolved, and whilst all other faecal samples were negative, her faecal calprotectin was elevated (>1,800). This therefore pointed towards an inflammatory process in the gastrointestinal tract as a cause of her diarrhoea. She was discharged 4 days after she was admitted, on oral steroids (60 mg once a day), gastro- and bone protection, six-hourly topical steroids, and cyclopentolate twice a day in both eyes.

At 1-week review post-discharge, she had greatly improved with the course of high-dose systemic steroids. Her VA was now 6/12 in both eyes, and all of the posterior synechiae had broken. There was no pupillary occlusion, and the iris bombe had completely resolved. On gonioscopy, the trabecular meshwork was visible, with Van Herrick grade 3 angles bilaterally, and an IOP of 10 mm Hg on either side. Furthermore, as shown in Figure 2b, the exudative detachments had resolved, both retinae were now flat, and there were only a few vitreous cells left. She was then slowly weaned off the systemic steroids (by 2-weekly 10-mg dose decrements until 40 mg, then 2-weekly 5 mg decrements), her topical cyclopentolate was stopped, and the topical steroids were tapered (by weekly 1 drop decrements).

Discussion

Alpelisib was first approved in the USA in May 2019 and was then approved by the European Medicines Agency in July 2020 [3, 5]. The recommended dose of alpelisib is 300 mg once daily taken with food. If the dose needs to be reduced due to adverse events, it is recommended to decrease it first to 250 mg once daily and then to 200 mg once daily. If dosage reduction below 200 mg/day is required, alpelisib should then be discontinued [3]. Drug-induced uveitis (DIU) is a rare, but important form of uveitis, which has been reported to have a prevalence of 0.5% in a tertiary uveitis referral centre [6]. Both direct and indirect mechanisms have been proposed to play a role in the pathogenesis of DIU. The direct mechanism is when the drug has a direct toxic effect by penetrating into the ocular tissues, typically occurring with topical, intravitreal, or intracameral drugs [7]. On the other hand, indirect mechanisms include a variety of drug-induced pathways such as immune complex deposition in the uveal tissues [8]. Recently, a mechanism which has come more into focus is immune-related adverse effects of immune pathway inhibitors. An example of this is checkpoint inhibitors, such as nivolumab, which have recently been developed as anti-cancer drugs. In fact, there are numerous reports of nivolumab-induced uveitis, including bilateral uveitis similar to our patient [9]. Other notable reported examples include tyrosine kinase inhibitors [10].

The diagnosis of DIU can be quite challenging since not only can the time taken for the offending drug to cause uveitis vary but also the same drug that causes uveitis in a cohort of patients might cause a different kind of inflammation, or indeed no inflammation, in other patients. In our case, the patient presented 4 and a half months after starting alpelisib. In DIU, the first step in making a diagnosis is to exclude other possible causes of uveitis, as we did in our case, through the use of blood investigations and imaging. A way of trying to
determine the relationship between a drug and uveitis is by using the criteria developed by Naranjo et al. [11].

The Adverse Drug Reaction Probability Scale developed by Naranjo et al. consists of 10 questions which can be answered as either “Yes,” “No,” or “Do not know,” with different point values (−1, 0, +1, or +2) assigned to each answer. The scores are then added, and the total obtained (ranging between −4 and +13) gives an indication as to the probability that the reaction is linked to the drug in question. The association is considered definite with a score of 9 or higher, probable with a score of 5–8, possible if the total is 1–4, and doubtful if 0 or less. A simplified version of the 10 questions is:

- Are there previous conclusive reports of this reaction?
- Did the adverse event appear after the drug was administered?
- Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?
- Did the adverse reaction reappear upon re-administering the drug?
- Are there alternative causes (other than the drug) that could on their own have caused the reaction?
- Did the adverse reaction reappear upon administration of placebo?
- Was the drug detected in the blood or other fluids in toxic concentrations?
- Was the reaction more severe upon increasing the dose? Or was the reaction less severe upon decreasing the dose?
- Did the patient have a similar reaction to the same or similar drugs in past exposures?
- Was the adverse event confirmed by any other objective evidence? [11].

In our case, the Naranjo score is 5, which would classify the association as “probable.” However, not all of the Naranjo criteria could be accurately answered since the drug was stopped without any dose alterations; it was not re-administered, no blood (or other fluid) drug level could be checked, no placebo was given, and no objective evidence was available. Therefore, the Naranjo score might actually be higher for alpelisib should all of the criteria be tested.

The mechanism as to how alpelisib could cause uveitis is unclear at this stage. However, the PI3K signalling pathway has been extensively studied over the past few years. PI3Ks are enzymes which mainly act on membrane-bound phospholipids, to generate specific molecular messengers in these membranes. The eight PI3Ks known to exist in mammalian cells are classified into three families: class I isoforms (PI3Kα, β, γ, δ), class II isoforms (PI3KC2α, β, γ), and a single class III isoform [12].

Class I PI3K signalling plays an intricate role in orchestrating both pro-inflammatory and anti-inflammatory pathways for effective B- and T-cell-mediated immunity [13]. In fact, studies show that both inhibition and hyperactivation of one of the main class I isoforms PI3Kδ results in defective adaptive immune responses [14]. The main PI3K isoforms expressed in T cells are PI3Kδ and PI3Kα [15]. A study performed by Stark et al. [16] showed that while loss of PI3Kδ alone in T-regulator cells does not lead to autoimmunity, combined loss of PI3Kα and PI3Kδ signalling resulted in increased severity of T-cell-driven central nervous system inflammation in mice. Moreover, mice lacking both isoforms in T-reg cells developed spontaneous peripheral nerve inflammation [16]. These results show that PI3K signalling, including PI3Kα, plays a significant role in T-reg cell-mediated protection against CNS inflammation. It could potentially mean that the mechanism of alpelisib-induced uveitis lies with its inhibition of PI3Kα, leading to dysfunction of this intricate pathway.

Similar to our case, other reported cases of immune pathway inhibitor-associated uveitis resolved with varying combinations of systemic steroids and/or topical steroids, with a quick recovery of visual acuity [17]. Our case report has a number of limitations. As mentioned previously, our Naranjo score is 5, which would classify the association as
“probable.” Unfortunately, not all of the Naranjo criteria could be accurately answered, and therefore, the Naranjo score might actually be higher for alpelisib should all of the criteria be tested. However, as DIU is rare even for tertiary centres, it is important for our experience to be shared with a global audience. This would encourage clinicians encountering similar patients to share their clinical experiences.

**Conclusion**

DIU remains a diagnosis of exclusion as it is important to rule out other possible and more common associations of uveitis. As immunotherapies targeting immune checkpoints and proteins remain important in the drug development pipeline for conditions such as breast cancer, it is important for clinicians and researchers to be vigilant for potential unexpected side effects of new medications. A potentially exciting and promising future for drug development and monitoring is machine learning for predicting the risk of drug-induced autoimmunity and adverse effects [18, 19]. This could potentially help researchers spot potential adverse effects early on and develop safer drugs. This case of alpelisib-induced uveitis highlights the importance of early ophthalmology involvement by the oncology team as new oncology therapy can have potential unexpected ocular manifestations.

**Statement of Ethics**

Ethical approval is not required for this case report in accordance with local and national guidelines. Written informed consent was obtained from the patient in question to publish their medical case and accompanying images.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Mr. Yu Jeat Chong was responsible for conception and design of the work, drafting the work and revising it critically for important intellectual content, and final approval of the version to be published. Dr. Matthew Azzopardi was responsible for conception and design of the work, drafting the work and revising it critically for important intellectual content, updating reference lists, and final approval of the version to be published. Dr. Mohammad Omar Tallouzi, Dr. David Spooner, Mr. Imran Masood, Mr. Yajati Ghosh, and Mr. Sreekanth Sreekantam were responsible for conception of the work, revising it critically for important intellectual content, and final approval of the version to be published. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Data Availability Statement

All data used during this study are included in this published article. Further enquiries can be directed to the corresponding author.

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