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A Case of Acute Retinal Necrosis Syndrome in a Bortezomib-Based Therapy Patient with Acyclovir Prophylaxis

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Abstract: The objective is to report a case of acute retinal necrosis (ARN) syndrome in a bortezomib-based therapy patient with acyclovir prophylaxis. A 61 years old Malay man with plasma cell leukemia, diabetes mellitus and hypertension, presented with 4weeks history of blurring of vision, photophobia and slight pain on the left eye. He had been under chemotherapy for plasma cell leukemia for the past 5 months consisted of bortezomib, cyclophosphamide and dexamethasone. Acyclovir prophylaxis was given to prevent reactivation of ARN. On examination, the left eye had visual acuity of 6/12 and the right eye had visual acuity of 6/9. There was no relative afferent pupillary defect. The left eye revealed high intraocular pressure of 44mmHg with 1+ of cells in the anterior chamber. Fundus showed a well-demarcated necrotic retina at the peripheral extended from 10-12 o'clock. It was associated with vitritis. The right eye had insignificant finding. A clinical diagnosis of left ARN syndrome was made and treated with intravenous acyclovir and followed by oral dose. The ARN initially showed slow recovery to the antiviral therapy until the bortezomib was was replaced by a substitute. Interestingly, his condition dramatically improved. The final visual outcome of the left eye was good and there were no complications or recurrence after three months of follow-up. Varicella-Zoster Virus (VZV) reactivation is one of the common complications encountered in the patients with bortezomib-based chemotherapy. However, there is limited data on ocular VZV reactivation in these patients. Numbers of reports have shown that this complication can be prevented by giving the acyclovir prophylaxis during the course of therapy, but it may still occur Hence, regular ocular examination is remained important.
Keywords: Bortezomib-based therapy, Acute Retinal Necrosis Syndrome, Acyclovir prophylaxis

INTRODUCTION

Acute retinal necrosis (ARN) is an uncommon clinical diagnosis which is characterized by acute inflammation of the vitreous, retina and its vessels, together with retinal necrosis [1]. Approximately 65% of all cases involve bilateral eyes; however, the risk of the fellow eye to be affected can be reduced by using acyclovir prophylaxis [1, 2]. The common causative organisms of ARN include Herpes Simplex virus (HSV), Varicella-Zoster Virus (VZV), Epstein–Barr virus (EBV), and Cytomegalovirus (CMV) [3-5, 7]. Patients with immuno compromised status such as chemotherapy, steroid treatment and acquired immunodeficiency syndrome (AIDS) are at a higher risk [6-7].

CASE REPORT

A 61 years old Malay man with plasma cell leukemia, diabetes mellitus and hypertension, presented with 4-weeks history of blurring of vision, photophobia and slight pain on the left eye. He had been under chemotherapy for plasma cell leukemia for the past 5 months consisted of bortezomib, cyclophosphamide and dexamethasone. He had a history of suprapubic herpes zoster lesion after the 3rd cycle of chemotherapy. He was treated with oral acyclovir 800mg 5 times daily for a week followed by prophylactic dose of 200mg twice daily.

On examination, the affected left eye had visual acuity of 6/12 and the right eye had visual acuity of 6/9. There was no relative afferent pupillary defect. The left eye revealed high intraocular pressure of 44 mmHg with 1+ of cells in the anterior chamber. Left fundus showed a well-demarcated, creamy-white necrotic retina at the peripheral extended from 10 to 12 o'clock (Figure.1). It was associated with vitritis but no vasculitis was seen. The right eye had insignificant finding.

A clinical diagnosis of left ARN syndrome was made. He was started on intravenous Acyclovir 500mg twice a day for ten days followed by oral acyclovir 200mg twice a day; the left eye developed

high intraocular pressure but was controlled with 2 anti-glaucoma agents, Gutt brimonidine three times daily and Gutt Timolol twice daily. The ARN initially showed slow recovery on fundus examination to the antiviral therapy and no improvement on his vision. (Figure 2) Therefore, the bortezomib was withheld and replaced by oral thalidomide 100mg daily but the oral Dexamethasone 40mg was continued. Interestingly, his condition dramatically improved, with minimal vitreous cells after the bortezomib was withheld (Figure 3). Prophylactic photocoagulation barricade laser was performed around the necrotic retina after obtaining the clearer fundus view to prevent retinal detachment.

After three weeks of treatment, there was no active retinitis or vitritis seen (Figure 4). After 3 months of follow ups, visual acuity of the left eye improved, with 6/9 vision. The retinal necrosis fully resolved with scar formation sparing the macula and there was no retinal detachment. The prophylatic acyclovir was continued.

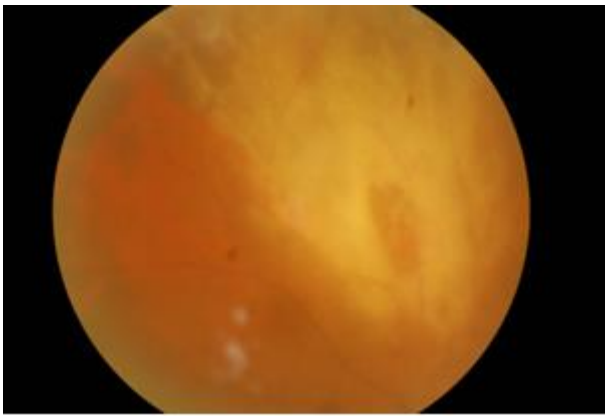

Fig. 1: A well-demarcated creamy-white necrotizing retinitis at superonasal quadrant

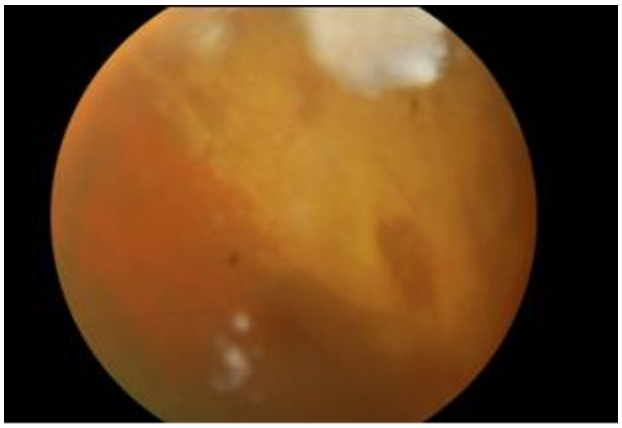

Fig. 2: On day 9 of systemic acyclovir treatment, showed some improvement with minimally reducing of the retinal necrosis

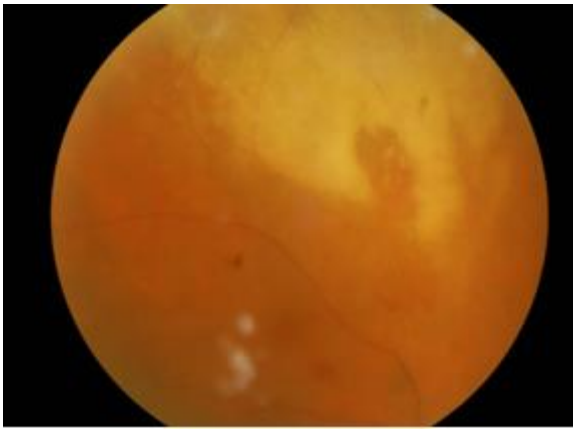

Fig. 3: On day 12 of treatment, the ARN size and density was reduced

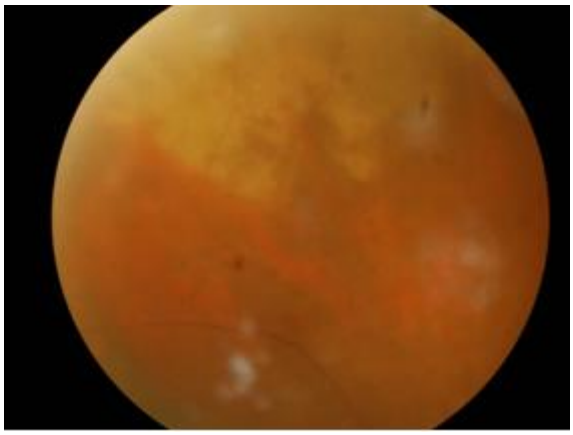

Fig. 4: ARN was improved after 3 weeks of anti-acyclovir treatment

DISCUSSION

Here we report a case of herpes zoster induced ARN despite oral acyclovir prophylaxis, in a bortezomib based chemotherapy plasma cell leukemia patient. In this case, the condition of the patient showed significant improvement especially after bortezomib was replaced by other substituent. Visual outcome of this patient was good without developing complications after three months of follow-up.

Plasma cell leukemia (PCL) is an uncommon but aggressive lymphoproliferative disorder. It is considered as a leukemic variant of multiple myeloma which is characterized by malignant proliferation of plasma cells in the bone marrow and circulating in peripheral blood. PCL is presented into 2 forms; primary and secondary. The primary form occurs in individuals without preceding multiple myeloma; and the secondary form arises from the pre-existing multiple myeloma. Treatments of plasma cell leukemia are chemotherapy and supportive care. Current chemotherapy agents include bortezomib, thalidomide, doxorubicin, cyclophosphamide and dexamethasone.

Bortezomib is a potent anti-cancer drug which acts as a selective proteasome inhibitor where it inhibits cell growth and gives an apoptotic effect on the tumor cell. It is also a very efficient drug that is used to treat PCL nowadays. However, one of its common adverse effects is reactivation of VZV. Although the mechanism of VZV reactivation remains unclear, it is believed that bortezomib tends to suppress the proliferation of T-cell, activation of CD4-positive T cells, and dendritic cell function, resulting in reduction of cell-mediated immunity (CMI) [8-10]. Furthermore, Kim et al. has recently reported that the VZV-specific CMI was significantly lower in patients who was treated with Bortezomib [18]. As CMI plays a larger role in preventing the reactivation of VZV than humoral immunity [11], the risk of reactivation therefore increases during bortezomib therapy, including herpes zoster ophthalmicus [12, 14]. The incident of VZV reactivation was reported up to 13% in bortezomib therapy when compared to 5% in dexamethasone group. [13] The risk, however, can be reduced by giving acyclovir prophylaxis during the course of bortezomib treatment [15, 16, 18]. A study showed none of the acyclovir prophylactic patients had developed herpetic reactivation during 4 years of monitoring [17].

Pour et al. have reported that the use of low-dose acyclovir prophylaxis with 400 mg once daily has similar effects in prevention of reactivation to the conventional dose, 400mg three times daily [19]. Recently, Kim et al. have once again showed the effectiveness of low-dose acyclovir in VZV protection [20]. In another study, prophylaxis was successfully done by using the ultra-low-dose acyclovir, 200 mg daily [21]. However, the exact dose and duration of prophylactic acyclovir remains uncertain.

Antiviral agents that were used to treat ARN include acyclovir, valacyclovir and famciclovir. Traditionally ARN was treated with intravenous acyclovir and followed by oral course. Valacyclovir is a prodrug with greater oral bioavailability than acyclovir. It will convert to acyclovir after absorption; therefore it is more efficient in treating VZV. Aizman et al. has reported the complete regression of ARN in all their patients after treated with oral valacyclovir [22]. However, a slow recovery of the ARN may occur during the course of bortezomib therapy. This can be due to the impaired host immunity system. Moreover, with the prolonged use of antiviral agents, the antiviral resistance may develop, and it can challenge the effectiveness of the antiviral therapy. Therefore, the modification of the chemotherapeutic agents has to be considered.

CONCLUSION

It is important to prevent the VZV reactivation by starting acyclovir treatment during the course of bortezomib chemotherapy. However, reactivation may still occur. Hence, it is more important to counsel and monitor the patients regularly as outpatients including proper fundus examination. Co-managing with the oncologists is important. A good visual outcome can

still be achieved if early clinical diagnosis is made and managed appropriately.

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