Inflammation and infection

The mysterious gross haematuria in patient on Leflunomide: A case report and literature review

Vincent Khor∗,1, LIE Kwok Ying

Urology Unit, Ng Teng Fong General Hospital, NUHS Singapore, 1 Jurong East Street 21, 609606, Singapore

Introduction

In 1998, the United States Food and Drug Administration approved Leflunomide for the treatment of active rheumatoid arthritis. Leflunomide is classified as a disease-modifying anti-rheumatic drug (DMARD), which has immunomodulatory, anti-inflammatory, analgesics and antipyretic effects. We report an atypical case of a 70-year-old lady presented with two isolated episodes of gross haematuria with mild thrombocytopenia, 5 months after she was started on Leflunomide.

Case report

A 70-year-old lady presented with 5-days of painless gross haematuria with some difficulty in micturition and was admitted to the Urology unit. She has normochromic normocytic anaemia (Haemoglobin [Hb]: 11.4 g/dL), hypertension and seropositive rheumatoid arthritis of which she was on Leflunomide, Sulfasalazine, prednisolone and monthly injection of Golimumab. She had no dysuria, fever, abdominal or flank pain. She had a similar episode 4 months ago which lasted for 6 days and resolved spontaneously. Physical examination was unremarkable. Initial laboratory investigations showed: Hb level of 8.9 g/dL (normochromic normocytic), mild thrombocytopenia with platelets count of 145 × 10³/L, with normal coagulation profile and renal function. Urine dipstick showed 3 + for blood, leucocyte and protein with positive nitrite. Urine culture was sent and she was put on continuous bladder washout (CBWO).

The Hb level dropped further to 7.6 g/dL in the next day and she required 2 units of packed cells blood transfusion. CT Urogram was performed and it showed bilateral hydroureteronephrosis with obstruction at the vesicoureteric junction where filling defects are seen in the bladder which resembled blood clots. Flexible cystoscopy performed but the vision was poor due to the haematuria. Over the following 4 days, the CBWO was persistently blocked and required gentle aspirations and multiple manual washouts. Platelet counts dropped to 125 × 10³/L on post-admission day 2 but raised to about 140 + and remained that level throughout the admission. Peripheral blood film showed reduced number of platelets with large platelets seen. Second flexible cystoscopy performed again on post admission day 4 but was unhelpful again due to the poor vision. CT Renal Angiography did not reveal any vascular malformation which could cause the haematuria. As the haematuria did not resolve, she was brought to the theatre for cystodiathermy and rigid cystoscopy. On rigid cystoscopy, we found that there was profuse neovascularization throughout the bladder [Fig. 1]. Small bleeding vessel from the posterior wall was cauterized. Clear urine jet was noted to be extruding from bilateral ureteric orifices. No papillary/CIS lesion noted in the bladder on both white light and narrow band imaging (NBI) mode. The haematuria resolved and she was discharged on post-operative day 1. Urine culture and cytology were negative.

When we reviewed her drugs and investigations history again, we found that her first episode of haematuria occurred 5 months after she was started on Leflunomide, and her platelets count dropped slowly to the level of her initial presentation to us. [Fig. 2] She has been taking prednisolone, hydrochloroquine and sulfasalazine since 2013, with no history of gross haematuria noted. She denied any history of radiation therapy as these neovascularization may be attributed to radiation. We made the hypothesis that Leflunomide was the cause of the abnormal neovascularization pattern seen in cystoscopy, and the bleeding from these vessels was related to the drug-associated thrombocytopenia. Leflunomide was then stopped after discussed with her Rheumatologist.

A repeat flexible cystoscopy 3 months later showed the similar neovascularization pattern with no active bleeding or bladder lesion [Fig. 3]. After the Leflunomide was stopped, she did not report any more episode of haematuria and the platelets count resumed to normal level.

Discussion

Leflunomide is used to treat adult patients with early or late active rheumatoid arthritis as DMARD. It is an isoxazole derivative, which acts as an immunomodulatory rather than immunosuppressive agent, and in addition have anti-inflammatory, analgesic and antipyretic effects. The immunomodulatory action is mediated primarily through the effect of
its metabolite, a malononitrilamide termed A177-1726, which is a non-competitive inhibitor of dihydro-orotate dehydrogenase, an enzyme required for de novo production of pyrimidine, and hence has anti-proliferative effect.1

We conducted a comprehensive PubMed/MEDLINE search and used reference lists from several articles to identify related articles which relate gross haematuria, bladder neovascularization with Leflunomide. There was a case report of gross haematuria associated with Leflunomide, which was due to its interaction with warfarin.2 Thrombocytopenia is an uncommon complication and is rarely significant, associated with the use of Leflunomide.3,4 Till date, there is no reported case on severe gross haematuria and neovascularization in bladder associated with the use of Leflunomide. Experimental study suggested that Leflunomide possesses anti-angiogenic activity.5 Waldman et al. shown that A77-1726 inhibits (i) vascular endothelial proliferation, (ii) multicellular organisation of endothelial cells into capillary-like anastomosing networks and (iii) sprouting and growth of microvessels from explanted segments of murine aorta.6 For this patient, we made the hypothesis that Leflunomide was possible cause of the profuse abnormal neovascularization pattern in her urinary bladder, based on the timeline shown above. The drug was stopped after discussion with her Rheumatologist. The thrombocytopenia resolved and the haematuria did not recur subsequently.

**Conclusion**

We could not find a reasonable explanation to describe the cause of this bladder neovascularization pattern. Although the literature showed that Leflunomide exerts anti-proliferative and anti-angiogenesis activities, but it might behave differently in-vivo or this might be a rare complication of Leflunomide which has not been reported yet. Based on the timeline and clinical course, we made the hypothesis that...
Leflunomide was the possible cause of this profuse bladder neovascularization pattern. Further properly-designed cohort studies are required to identify whether DMARD especially Leflunomide, could cause this type of bladder neovascularization and gross haematuria.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eucr.2018.10.012.

References

1. Rozman B. Clinical pharmacokinetics of Leflunomide. Clin Pharmacokinet. 2002;41(6):421–430.
2. Lim V, Pande I. Leflunomide can potentiate the anticoagulant effect of warfarin. BMJ. 2002;325(7376):1333.
3. Li EK, Tam LS, Tomlinson B. Leflunomide in the treatment of rheumatoid arthritis. Clin Therapeut. 2004;26(4):447–459.
4. Leflunomide (Arava). Prescribing Information. Sanofi-Aventis U.S. LLC; 2016.
5. Waldman W, Bickerstaff A, Gordillo G, Oroz C, Orosz K, Knight D, Orosz C. Inhibition of angiogenesis-related endothelial activity by the experimental immunosuppressive agent Leflunomide. Transpl Hematol. 2001;72(9):1578–1582.