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OLGU SUNUMU / CASE REPORT

Adverse drug reaction reporting on eosinophilia secondary to thalidomide therapy in Lepra type 2 reactions: a mandate responsibility

Lepra tip 2 reaksiyonlarında talidomid tedavisine ikincil eosinofili ile ilgili rapor edilen ilaç yan etkisi: zorunlu bir sorumluluk

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Abstract
Limited data are available on eosinophilia as a drug adverse event with immunosuppressant and modulator. We report a case of 40 year old male patient treated with thalidomide for lepra reaction developed thalidomide induced eosinophilia. Eosinophil count rose during thalidomide treatment and decreased in the periods when the patient was off the treatment. Eosinophilia as an adverse event due to thalidomide has been described rarely except in a case of congener Lenalidomide. This case shows a clear temporal relationship between thalidomide and eosinophilia. With reference to this case, monitoring of patients receiving similar treatment can be increased to detect and prevent any possible adverse drug reactions before it adds up to the suffering of the patient in turn improving the quality of medical services and patient care as well. Thus the quality has been improved and managed in the current case.
Keywords: Adverse event, thalidomide, eosinophilia

Öz
İmmunsüpresif ve modülatör ilaçların yan etkisi olarak eozinofili bildirimi konusunda sınırlı veri mevcuttur. Bu yazıda lepra reaksiyonu nedeniyle talidomid ile tedavi edilen, talidomide bağlı eozinofili gelişen 40 yaşında bir erkek hasta sunulmuştur. Talidomid tedavisi sırasında eozinofil sayısı yükseldi ve hastanın tedavi dışında olduğu dönemlerde azaldı. Talidomide bağlı advers bir olay olarak eozinofili, bir türdeş Lenalidomid vakası dışında nadiren tarif edilmiştir. Bu olgu, talidomid ile eozinofili arasında açık bir nedensel ilişki olduğunu göstermektedir. Bu olgu bağlamında, benzer tedaviyi alan hastaların izlenmesi olası tıbbi hizmetlerin kalitesini ve hasta bakımını artırarak hastanın acı çekmesine neden olmadan önce olası herhangi bir yan etkiyi tespit etmek ve önlemek için arttırılabilir. . Bu şekilde mevcut olguda yaşam kalitesi iyileştirildi ve yönetildi.

Anahtar kelimeler: Yan etki, talidomid, eozinofili

INTRODUCTION

Eosinophilia is defined as increased number of eosinophils in peripheral blood around >500/mm3.This increase can be caused by intrinsic hematologic diseases, drugs and allergens.[1] Immunological reactions to drugs and drugs components could be a cause of eosinophilia, which is usually associated with diverse manifestations. One such manifestation occurs as diffuse maculopapular rash or other as drug rash with eosinophilia and systemic symptoms (DRESS).[2] Drugs most commonly associated with eosinophilia are antibiotic penicillin, sulpha drugs, antiepileptic phenytoin, carbamazepine, anti-gout allopurinol, and gold salts. Thalidomide is an immunomodulatory drug, approved to treat several haematological disorders such as multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma and in severe cases of erythema

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nodosum leprosum (ENL) reaction[3]. Eosinophilia secondary to thalidomide has rarely been described in management of leprosy reaction. Here, we describe a case report of a patient who suffered eosinophilia as a result of treatment with thalidomide.

Table 1. Published literature on eosinophilia by thalidomide and congener.

No	References	Indication	Medication	Inference
1	Tilluckdharry, Dean, Fsryer & Ahmad, 2008.[4]	Multiple myeloma	thalidomide	Eosinophilia pneumonia
2	Pretz &Medeiros, 2009.[5]	Plasma cell leukaemia	thalidomide	Eosinophilic pneumonitis
3	Foti et al,2012.[6]	Multiple myeloma	lenalidomide	DRESS
4	Sekiguchi et al 2014.[7]	Multiple myeloma/lung cancer	lenalidomide	Eosinophilia
5	Escudero-Vilaplana V et al 2017.[12]	Multiple myeloma	lenalidomide	Eosinophilia

CASE

A 40-year-old man was referred for the management of type 2 severe erythema nodosum leprosum at Central leprosy institute. The Patient was on regular medication with oral steroids tablet Prednisolone 30 mg in the morning, tablet Aceclofenac with paracetamol combinations on and off for the painful nodular episodes, antigastric tablet Omeprazole20 mg two times a day, and supplements multivitamins, calcium and antianxiety drug alprazolam 0.25 mg at night time. No known drug allergies or toxic habits were recorded.

At the time of admission, the main haematological parameters are haemoglobin 12.0 g/dL, platelet count 2.85 lakhs/cu mm, total leucocytes count of 11700 cells/cu mm with polymorphs 70%, Eosinophil 3%, lymphocytes 12%, monocytes 5%, basophilis 0% and absolute Eosinophil count of 48/cu mm. There were no significant alterations in any of the biochemical parameters. Consequently, severe type 2 ENL reaction diagnosis was retained, and treatment with current existing medications were continued with additional antibiotic for a week.

Since the patient not responded to the current medication an addition of capsule thalidomide was initiated with dose of 300 mg. The patient responded with improvement in symptoms within 48 hours. The treatment was continued with the same dose for 15 days. In spite of very good medical and nursing services, during the treatment course the patient developed intense generalized itching with macula papular rashes which was observed and reported by the nursing staff.

Since the patient was also on steroids for long period he has been investigated for possible fungal infection, but found to be negative.

Investigations are within normal range except for absolute Eosinophils count with marked increase to 2876/cumm from baseline value of 48/cumm. Since the patient needs thalidomide as he was responding with the drug, we could only able to reduce the dose to 200 mg with support of antihistamines. But the patient was not fully benefitted with antihistamines. Repeated absolute Eosinophil count showed a decreased value of 1073/cumm per 100 mg reduction. So after discussion among the whole therapeutic team (which includes the treating consultant, nursing, pharmacist, and dietician) we correlated the influence of drug and dose. Since the patient was a case of Lepra reaction, we have further reduced to 100 mg for 14 days and stopped after 15 days. The absolute eosinophilic count also reached normal. During this period the steroids were also tapered and stopped accordingly as there is no rationale indication to start it. Also clofazimine has been started for type 2 reaction at a dose of 300 mg to wean steroids and thalidomide.

Since the patient again developed reaction, we started tablet Thalidomide again at 100 mg daily for 15 days during which there was an increase in absolute eosinophils count again showing its direct correlation. The patient was managed simultaneously for reaction with clofazimine, alternate dose of thalidomide and with anti-histaminic and moisture lotion. The patient was assured regarding the stoppage of thalidomide once the clofazimine action will be started. The patient was currently under treatment for reaction and regular follow up.

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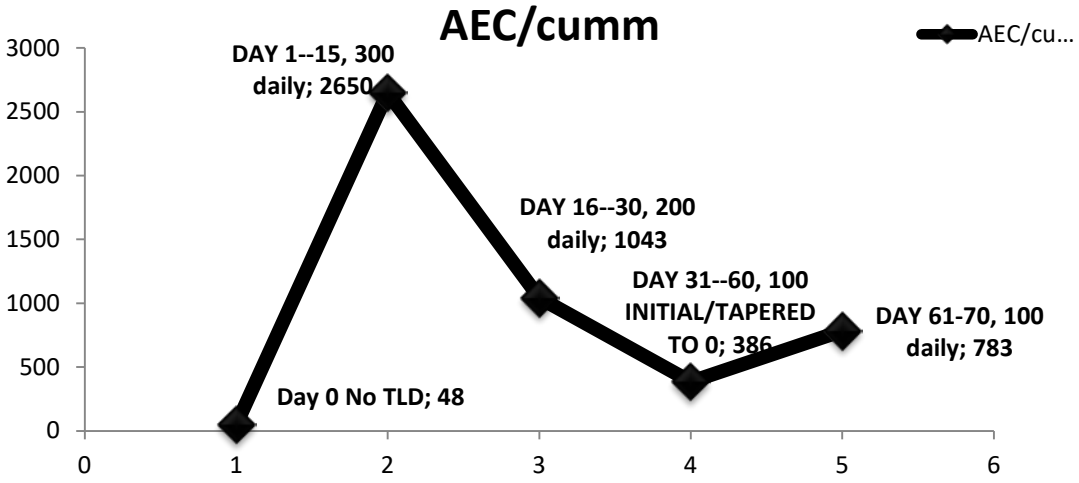

Figure 1. Various time line with respect to days, drug dose and absolute eosinophils count.

DISCUSSION

There are a handful studies /case reports available from around the world about immunomodulatory drugs induced eosinophilia. An extensive literature survey could serve only 5 primary references which were found relatable/closely related to our case report. The first 2 case reports regarding thalidomide induced eosinophilia were observed and published, but unlike our case report which is about a patient suffering from infectious condition, in both the cases the patients were under antineoplastic treatment and eosinophilia was seen localized only in the lungs. [4, 5] The rest 3 case studies reported were about Lenalidomide induced eosinophilia and DRESS. Also all the 3 patients were under antineoplastic treatment.[6,7,8] This case report is the first report from India (best known to our knowledge) in which a direct correlation between thalidomide use and development of eosinophilia can be observed. During hospitalization, most frequent causes of eosinophilia like allergic reaction, tropical parasitic disease and adrenal insufficiency were ruled out by IgE, microfilaria, serum cortisol investigations in our patient. Eventually, the Naranjo nomogram showed a probable correlation between eosinophilia and the use of thalidomide (score 8 out of 13)[9]. The event was notified to the Indian pharmacovigilance system given that it is extremely rare.

Our case demonstrates a clear correlation between eosinophilia and thalidomide drug treatment in severe erythema nodosum leprosum. Our study is the first to show that correlation in infectious related lepra reaction. Where as all other studies available in literature showed the similar eosinophilic condition by immunomodulatory drugs used in the management of cancerous conditions.

This substantial increase of eosinophils above the normal level (500/cumm) known as eosinophilia should be considered as one of the rare adverse effects of immunomodulatory drugs like thalidomide and should be labelled in drug information. At present very few reports have been cited regarding this rare effect of thalidomide therapy and most of them have reported a "Probable" causal relationship between eosinophilia and thalidomide, similar relationship was observed in our case according to Naranjo algorithm.[9]

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Patient's eosinophil count which was found to be very high above the normal level during the first 15 days of thalidomide treatment gradually decreased/depreciated with gradual tapering down the dose from 300mg/day to 0 (zero/day) during the next consecutive 2 weekly intervals.

It was observed that the eosinophil count again became normal during the week in which the patient was not receiving thalidomide therapy. This case report focuses especially on directly proportional dose dependent relationship between thalidomide treatment and eosinophil count.

Unlike teratogenicity and venous thromboembolism which are well known severe and serious adverse effects of thalidomide use, eosinophilia and its complications are rare adverse effects which are either under reported or unidentified in many cases. Thalidomide is still used in India in the management of Lepra reaction. In this case the drug induced eosinophilia manifested as severe itching all over the body, was an additional burden on the patient as well as on the clinical management team and we consider this case as a perfect signal to increase monitoring of such patients to detect, avoid and prevent any such ADRs as early as possible.

The exact mechanism of eosinophilia after thalidomide treatment is still unclear, although the immunomodulation properties of this drug may be involved. A possible mechanism for Lenalidomide which is a congener of thalidomide may be used for discussion purpose. As per the mechanism, thalidomide may also provide co-stimulation of both human T cells as well as Natural Killer T cells; consequently, the production of several cytokines is activated. Natural Killer T cells and the cytokines interleukin-6 could have effects on diverse innate cells including eosinophils.[10]

Apart from the above possible mechanism the salt used in the preparation by the pharmaceutical could also trigger allergic like reaction causing the allergen cells eosinophils to be increased.[11] But there is no clinical or laboratory evidence to substantiate this correlation and could be one aspect of suspicion. But it is definite that the trigger must be a strong stimulus that has orchestrated the whole allergic responses.

This was purely a retrospective observational finding during which the patient was being treated for the Lepra reaction with thalidomide. Complete Blood Counts (CBC) record was one of the routine laboratory tests recommended for the patient to supervise the effectiveness of the current treatment. Changes in the eosinophil count were noticed later when the patient was being discharged after recovery from the Lepra reaction.

Yazar Katkıları: Çalışma konsepti/Tasarımı: PT, SV, DNC, SBV; Veri toplama: PT, SV, DNC, SBV; Veri analizi ve yorumlama: PT, SV, DNC, SBV Yazı taslağı: PT, SV, DNC, SBV; İçeriğin eleştirel incelenmesi: PT, SV, DNC, SBV; Son onay ve sorumluluk: PT, SV, DNC, SBV; Teknik ve malzeme desteği: PT, SV, DNC, SBV; Süpervizyon: PT, SV, DNC, SBV ; Fon sağlama (mevcut ise): yok.
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