

CASE STUDY

G-CSF enables completion of tuberculosis therapy associated with iatrogenic neutropenia

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G-CSF enables completion of tuberculosis therapy associated with iatrogenic neutropenia. L.J. Cormican, S. Schey, H.J. Milburn. ©ERS Journals Ltd 2004.

ABSTRACT: Neutropenia is a rare complication of anti-tuberculous therapy and is usually due to a single agent, most frequently isoniazid. The current case describes a previously healthy immunocompetent patient with tuberculosis of the lymph nodes who developed neutropenia due to a number of first line antibiotics (rifampicin, isoniazid and ethambutol) and streptomycin when introduced in combination and individually thus resulting in repeated treatment disruption.

The introduction of twice-weekly subcutaneous granulocyte-colony stimulating factor to correct iatrogenic neutropenia facilitated the continuation and eventual completion of therapy without adverse effect.

This is the first description of the use of granulocyte-colony stimulating factor to correct iatrogenic neutropenia due to anti-tuberculous antibiotics and the second description of the occurrence of iatrogenic neutropenia to more than anti-tuberculous antibiotic in an individual. *Eur Respir J 2004; 23: 649–650.*

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Neutropenia in an immunocompetent patient is a recognised though rare complication of anti-tuberculous therapy. When associated with sepsis neutropenia carries a significant associated morbidity and mortality.

In the context of anti-tuberculous therapy, neutropenia is recognised as being most frequently due to isoniazid [1–3], but it can occur with rifampicin [4], ethambutol [1, 5] and streptomycin [6]. In the vast majority of cases during anti-tuberculous therapy, the occurrence of neutropenia is due to a single agent. By re-challenging the patient with each antibiotic individually, the offending drug can be identified, subsequently omitted and therapy completed using an alternative first or second line antibiotic if necessary.

Rarely has neutropenia been described as occurring due to more than one anti-tuberculous antibiotic in the same patient [1].

The current study presents a case of neutropenia due to four anti-tuberculous antibiotics. This was confirmed by individually re-challenging the patient with each antibiotic. Support with granulocyte-colony stimulating factor (G-CSF) was eventually employed, enabling the safe and successful completion of therapy.

Case history

A 30-yr-old asymptomatic Asian male presented with a 4 cm nontender lymph node at the base of his left anterior triangle, which was solid, nonfluctuant and fixed to the underlying tissues. Otherwise no abnormality was noted. Full blood count, white cell count differential, renal function, liver function tests and chest radiograph were entirely normal. A human immunodeficiency virus (HIV) test was negative.

A fine needle aspirate demonstrated acid-fast bacilli. The patient was commenced on rifampicin, isoniazid, pyrazinamide and ethambutol (weight adjusted) in accordance with local and national guidelines. Treatment was well tolerated and the patient reported to be fully compliant.

After four weeks of therapy, routine investigations revealed neutropenia, ($0.7 \times 10^9 \text{ L}^{-1}$) with a normal haemoglobin and platelet count. The patient had a 10-day history of a sore throat, was afebrile and had an unremarkable clinical examination except for the lymph node described above, which had not reduced in size. All anti-tuberculous antibiotics were discontinued.

Two weeks later on recovery from neutropenia, antibiotics were introduced individually and subsequently in combination unless neutropenia occurred (fig. 1). Ethambutol was introduced initially but resulted in neutropenia after 1 week and was discontinued. Upon recovery 2 weeks later, pyrazinamide was re-introduced and was well tolerated in terms of neutrophil count. Isoniazid was then re-introduced after a further 2 weeks. This combination was tolerated for 3 weeks when neutropenia recurred. Isoniazid was discontinued, as it was the most recently introduced agent. However, neutropenia persisted necessitating the discontinuation of pyrazinamide 2 weeks later. Cultures by then confirmed fully sensitive *Mycobacterium tuberculosis*.

Neutropenia persisted for a further 7 weeks in the absence of treatment, although the patient was asymptomatic and his lymph node had reduced in size.

Rifampicin and pyrazinamide were then re-introduced in combination but neutropenia again recurred after a week. In view of his recent history of tolerance of pyrazinamide for 4 weeks (week 9 to 13 of treatment), rifampicin was felt to be the most likely cause of neutropenia and was hence discontinued. Streptomycin IM was added to pyrazinamide on week 25 of treatment but neutropenia worsened after one week (neutrophil count dropped from 0.7 to $0.5 \times 10^9 \text{ L}^{-1}$). Both drugs were thus discontinued because of the risk of development of a drug resistant organism.

The patient was commenced on subcutaneous G-CSF (SC G-CSF) 105 *i.u.* on alternate days with recovery from neutropenia. Ethambutol was re-introduced in incremental

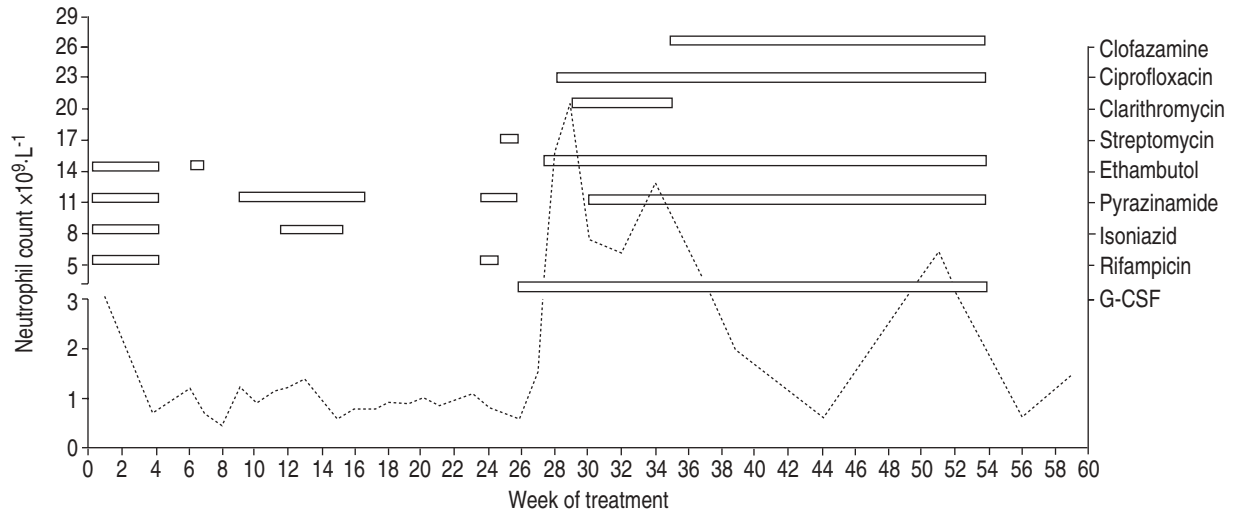


Fig. 1.—Graphic representation of the patients neutrophil count ($\times 10^9 \text{L}^{-1}$) and medications administered over the period of the treatment. G-CSF: granulocyte-colony stimulating factor.

doses without the development of neutropenia. The subsequent antibiotics were chosen to minimise any potential neutropenic burden on the patient. Rifampicin and isoniazid were not introduced because of their association with neutropenia [1–4], as had occurred on previous re-challenges. On a weekly basis over the next 3 weeks, ciprofloxacin, clarithromycin and subsequently pyrazinamide were introduced without the development of neutropenia. These agents were chosen, as neutropenia was not a recognised side-effect of their use. Clofazimine on alternate days was substituted for clarithromycin after 6 weeks of therapy because of recalcitrant nausea without adverse effect. Clofazimine was chosen, as it is one of the less likely of the second line anti-tuberculous antibiotics to cause neutropenia.

Due to the inadequacy of the patient's therapy and the risk of development of a drug resistant strain, a decision was made to treat him for a period of an additional 5 months with four antibiotics, thus completing a full year of therapy. It was not possible to re-culture the organism to determine a change in antibiotic sensitivity pattern as his lymphadenopathy had resolved. Extending the duration of therapy for any longer would have necessitated continued support with G-CSF. As there was no literature regarding the prolonged use of G-CSF in the situation of iatrogenic neutropenia in tuberculosis therapy, and given the fact that the patient had recovered from his original infection, a decision was made to limit the duration of therapy to 1 yr.

Discussion

Leucopenia, but rarely neutropenia have been reported following treatment with isoniazid [1–3] rifampicin [4], ethambutol [1, 5] and streptomycin [6]. The occurrence of neutropenia to more than one anti-tuberculous antibiotic in the same individual has been described only once [1] (rifampicin, isoniazid and ethambutol in combination and individually), with eventual maintenance achieved by the administration of prednisolone.

The present case is the only one in the literature of neutropenia occurring in response to treatment with four anti-tuberculous antibiotics (rifampicin, isoniazid, ethambutol and streptomycin). Furthermore it is the only report in the literature of a patient completing a course of anti-tuberculous treatment complicated by neutropenia with the use of G-CSF. The long-term administration of G-CSF is an accepted

therapy for congenital neutropenia and chronic idiopathic neutropenia [7]. Though evidence suggests that G-CSF does not reduce the frequency of infections in afebrile patients undergoing chemotherapy (for nonmyeloid tumours) [8], the current authors believe that its use in this case was justified because of the possible development of drug resistance as treatment was necessarily interrupted so often. The current authors consciously tried avoiding the use of monotherapy but this was not always possible when re-introducing drugs and it would not have been possible to treat the organism without some means of supporting his neutrophil count. Furthermore, G-CSF was employed in this regard as an alternative to prednisolone as it enabled titration of the dose to the patient's neutrophil response without the additional potential immunosuppressive effects of corticosteroids in a patient who was by that point (26 weeks postpresentation), inadequately treated.

This report demonstrates that neutropenia can occur due to more than one individual anti-tuberculous drug in a patient, and that the concomitant use of granulocyte-colony stimulating factor is safe and effective in situations where anti-tuberculous medications have to be continued when they are known to result in neutropenia.

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