



# **Paradoxical reactions in a patient under treatment for multidrug-resistant tuberculosis. A case report**

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## Abstract

Some patients with tuberculosis (TB), after starting treatment, may suffer an enlargement of their initial lesions (tuberculomas, adenopathy) or the development of new ones after some days or weeks on treatment. We describe a patient with primary resistance to several anti-TB medications (MDR-TB) and not infected with the human immunodeficiency virus (HIV). During the first weeks of treatment he developed marked enlargement of the cervical adenopathy which remitted after some weeks.

Algunos pacientes con tuberculosis (TB), después de unos días o semanas de recibir tratamiento anti-TB, pueden desarrollar nuevas adenopatías o un aumento de tamaño de las lesiones (tuberculomas, adenopatías) detectadas al inicio. Describimos un enfermo con resistencia inicial a diversos medicamentos anti-TB (MDR-TB) que no estaba infectado por el virus de la inmunodeficiencia humana (VIH). Durante las primeras semanas desarrolló un aumento de tamaño importante de las adenopatías cervicales que remitieron semanas más tarde.

**Key words:** Multiresistant-tuberculosis, Paradoxical reaction, HIV

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## Introduction and Case description

A 26-year-old male from Nepal was referred to our TB Centre from a general public hospital in Barcelona with a diagnosis of bilateral cervical adenopathies. The patient had lived in Spain for the past three years and worked as a cook. There was no recent history of contact with a person with TB but his father, who remained in Nepal and had died from haemoptysis. His medical history was non-remarkable; he had never received anti-TB treatment. He suffered during some

weeks before admission weakness, low grade fever and a non-productive cough. He had noticed a progressive swelling in both sides of his neck. Vital signs on admission were within normal limits. Physical examination revealed multiple bilateral cervical and supraclavicular nodes soft and tender, some as large as 10 x 6 cm; there were no axillary or inguinal nodes; the chest was clear on auscultation and no abnormalities were detected in the chest X-ray. Results of basic laboratory investigations (AAFB smear of the pus for AAFB and culture) were normal, including the HIV test. Several sputum

samples for acid and alcohol fast bacilli (AAFB) smears were all negative.

### Case Management

The patient was started on isoniazid, rifampicin, ethambutol and pyrazinamide. A polymerase chain reaction (PCR) and an AAFB smear of the pus were positive for AAFB. Subsequent cultures revealed AAFB resistant to isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin. The therapeutic regimen was changed to PAS, pyrazinamide, moxifloxacin, and cycloserine orally and capreomycin by injection<sup>1</sup>. After a few days on treatment the

right cervical mass had swollen and began to drain (Fig.1); steroids were added (30 mg of prednisone/day). Weeks later, new adenopathies appeared on the left side (Figure 2). The cervical nodes on both sides drained twice and eventually closed after a few weeks. The patient suffered from paresthesias in both legs which disappeared after a short course of oral pregabalin. After 22 months on such treatment the patient was discharged; he had no further complains and the cervical and supraclavicular nodes had disappeared. We were unable to follow his course as he returned to his home country.



Figure 1 Swollen cervical mass



Figure 2 new adenopathy

Figure 1. View of the patient's neck shortly after admission.

Figure 2. Left side of the patient's neck after several weeks on treatment.

<sup>1</sup> New anti-TB agents such as linezolid and bedaquiline were not easily available at the time.

## Case findings

Our patient was Nepalese, a country with few resources (Human Development Index: 149) and with a high annual incidence of TB ( $111 \times 10^5$ ). He presented with MDR-TB; he had never received TB treatment and there was no known TB contact, although his father might have died of TB some years before in the patient's country of origin. MDR-TB is a worldwide growing problem which poses serious therapeutical difficulties for achieving cure; about 153 000 cases were detected in 2017 (1). After knowing the results of the antibiogram the drug regimen, after a few days of treatment with anti-TB primary drugs, was changed to several second line medications. In view of the undulant clinical course steroids were added and administered for three months.

## Case Discussions

An article before the HIV epidemic described seven immigrant patients in the United Kingdom with adenopathies, two patients developing them while on anti-TB treatment or having abandoned it; they also had pulmonary or pleural tuberculosis (2). A study from a TB hospital in Florida divided

the patients into three groups: HIV-infected on anti-TB treatment and antiretroviral (ARV) drugs; HIV infected patients only on anti-TB medications; and HIV negative patients on anti-TB treatment. Paradoxical reactions were more frequent in the group of patients who were on treatment for both TB and HIV. The authors suggested that these reactions may represent an immune response enhanced by the ARV medications (3).

HIV infected patients tend to develop paradoxical reactions during the early phase of TB treatment and some authors state that it is more frequent among those with more significant immune restitution and concomitant reduction of the viral load (4). The association between ARV treatment and anti-TB treatment has been reported by other authors. Breen et al. suggested to postpone the initiation of ARVs, especially in the presence of disseminated TB (5). A large study from South Korea found that among patients with peripheral lymph nodes TB paradoxical reactions were not unusual and occurred at a median of eight weeks after starting treatment (6); in a significant proportion, like in our patient, the nodes drained spontaneously and several patients developed new ones; younger age, male sex

and local tenderness at diagnosis were all associated with reactions; more than half of the patients had a spontaneous resolution without the addition of steroids.

A case of a female patient from India was published by Kant (7). She presented with bilateral cervical adenopathies with multiple draining sinuses; she was HIV negative and resistant to the anti-TB primary drugs (MDR-TB). After 18 months of treatment with six second line medications the patient was declared cured. A woman from Bangladesh living in the United States for several months had a history of cervical nodes for two years which drained spontaneously while on TB treatment; she was HIV negative; prednisone was added and the patient improved. No mention was made whether an antibiogram was obtained (8). A retrospective study from a group in South Korea determined that among 467 patients not HIV-infected 18 % suffered a paradoxical reaction. Reactions were more frequent in patients with extra-pulmonary TB; 7 % had lymph node enlargement after completing anti-TB therapy (9). The authors felt it was not necessary to prolong treatment for these reactions to improve

## **Case Contribution to sustainable development**

This case report may have laid out the framework for clinical observations of idiosyncratic response of first line drugs used in clinical management of diseases of a globally significant public health concern (8). This framework opens a new and basic research horizon for conventional full-length papers to ask relevant questions as they get engaged in designing similar researches in the same field. While providing clinical advantage to disease management it will help improve recovery confidence of those affected with similar diseases today and in the foreseeable future

## **Case Limitations**

This study has the normal general limitations usually attributed to all case reports. Like all case reports, this study had no rigorous scientific labor, had limited bases for generalization of the observations, difficult to replicate, authors bias could not be ignored. It was time consuming and costly

## Case Conclusions and recommendations

The aetiology of these reactions has not been completely clarified and several mechanisms have been proposed: host immune reactions such as a delayed hypersensitivity response to mycobacterial antigens, a decrease in immune suppression, and a change in the immune response to TB proteins (8). Recently, the administration of prophylactic steroids in HIV infected patients has been proposed in order to prevent the immune reconstitution inflammatory syndrome (IRIS) in patients with TB initiating ART (10).

## Author contribution

JEO-G wrote the paper. All authors took care of the patient and revised the manuscript.

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## Conflict of interest

The authors declare no conflict of interest

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