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# Paradoxical deterioration during anti-tubercular treatment in a dialysis patient on maintenance steroid therapy

## 接受透析和類固醇康復治療的病人在接受抗結核治療時出現病情反常惡化

We report a 38-year-old Chinese woman with lupus nephritis on peritoneal dialysis and long-term maintenance steroid therapy. This patient developed paradoxical deterioration during anti-tubercular therapy for tuberculous lymphadenitis. The deterioration resolved spontaneously without change to pharmacotherapy. Paradoxical deterioration that may spontaneously resolve is a potential complication of anti-tubercular treatment in patients on long-term renal replacement therapy.

本病例報告一名38歲華裔女性病人患有狼瘡性腎炎，須接受腹膜透析以及長期類固醇康復治療。在因染上結核性淋巴結炎而接受抗結核治療的過程中，病情反常惡化。在無需藥物治療的情況下，病情最後停止惡化。長期接受洗腎治療的病人，在接受抗結核治療時，可能會出現病情反常惡化而可以自動停止的併發症。

### Key words:

Antitubercular agents;  
Peritoneal dialysis;  
Steroids;  
Tuberculosis

### 關鍵詞：

抗結核藥劑；  
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### Introduction

Paradoxical deterioration during anti-tubercular therapy refers to the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions not attributable to the normal course of disease in a patient who initially improves with anti-tubercular therapy.<sup>1</sup> This phenomenon is more commonly associated with extrapulmonary tuberculosis.<sup>2</sup> There is no specific diagnostic test for such paradoxical deterioration, although a surge in lymphocyte count is suggestive of such a diagnosis.<sup>2,3</sup> Paradoxical worsening during treatment for tuberculosis has been extensively reported in AIDS patients, particularly following therapy with highly active antiretroviral agents.<sup>3-5</sup> It is also well recognised in patients without HIV infection.<sup>1,2,6-8</sup>

Patients with chronic renal failure are more prone to opportunistic infections, including tuberculosis.<sup>9-11</sup> In patients undergoing continuous ambulatory peritoneal dialysis (CAPD), the prevalence of tuberculosis is several times higher than that of the general population.<sup>10</sup> Nonetheless, a paradoxical response during anti-tubercular therapy has not been reported in such patients and has not, apparently, been previously described in patients receiving long-term steroid therapy. We report a patient with underlying lupus nephritis on CAPD and maintenance steroid therapy who demonstrated a paradoxical deterioration during treatment for tuberculous lymphadenitis.

## Case report

The patient was a 38-year-old Chinese woman with end-stage renal failure secondary to lupus nephritis who commenced haemodialysis in 1995. In March 2002, she switched to CAPD because of failed vascular access. A history of cerebral lupus was noted for which long-term maintenance steroid therapy was prescribed (prednisolone 5 mg daily). Lupus activity had been clinically and serologically inactive following commencement of renal replacement therapy.

In September 2002, the patient presented with fever and appearance of a left upper neck swelling. Physical examination revealed enlarged left upper cervical lymph nodes. No other lymph nodes were affected, nor were the liver or spleen. Preliminary investigations revealed the following: normal total white cell count ( $4.4 \times 10^9$  /L) with relative lymphopenia ( $0.6 \times 10^9$  /L), haemoglobin level of 67 g/L, and platelet count of  $90 \times 10^9$  /L. Erythrocyte sedimentation rate was 32 mm/h and C-reactive protein was elevated at 34.4 mg/L (reference level, <7.6 mg/L). Serum electrolytes and liver function tests were unremarkable. Serum albumin and globulin levels were 23 g/L and 40 g/L, respectively. Her lupus serology was quiescent: antinuclear factor titre 1/160, anti-DNA titre less than 1 IU/mL (reference range, 0-35 IU/mL), complement levels normal (C3, 1140 mg/L [reference range, 760-1500 mg/L]; C4, 300 mg/L [reference range, 90-350 mg/L]). She was seronegative for HIV. Chest radiography revealed clear lung fields and nasal endoscopy was normal. Fine needle aspiration of the left cervical lymph node yielded several millilitres of pus-like material. Smear examination and culture of the aspirate was negative for bacteria and acid-fast bacilli. Cytology was negative. Excisional biopsy of the cervical lymph node revealed granuloma formation, extensive caseous necrosis, and the presence of acid-fast bacilli by Ziehl-Neelsen stain. A diagnosis of tuberculous lymphadenitis was made and the patient was given supervised anti-tubercular therapy (daily doses of isoniazid 200 mg, rifampicin 450 mg, pyrazinamide 1.5 g, levofloxacin 200 mg, and pyridoxine 100 mg). Cultures of the aspirate and excisional biopsy from the left cervical lymph node subsequently yielded *Mycobacterium tuberculosis* that was sensitive to standard anti-tubercular drugs. The patient was maintained on the existing 5 mg per day oral prednisolone. The enlarged cervical lymph nodes decreased in size after the initiation of anti-tubercular therapy, but increased again along with tender right axillary lymphadenopathy 2 weeks later. Total white cell count at the time was normal but lymphocyte

count had increased to  $1.4 \times 10^9$  /L. Fine needle aspiration of the right axillary lymph node revealed acid-fast bacilli on smear, although subsequent bacterial culture was negative. Lupus serology remained stable and a provisional diagnosis was made of paradoxical deterioration. Anti-tubercular and steroid therapy was continued. Cervical and right axillary lymph nodes decreased in size after a week and completely resolved 3 weeks later, and the patient's general condition gradually improved. Anti-tubercular drug therapy was completed uneventfully and maintenance steroid therapy continued.

## Discussion

We report a lupus patient on CAPD and maintenance steroid therapy who developed paradoxical deterioration during treatment for tuberculous lymphadenitis. The paradoxical deterioration resolved spontaneously with continuation of anti-tubercular drugs and with no change in steroid dosage.

Paradoxical deterioration during anti-tubercular treatment is diagnosed by exclusion. Enlargement of cervical lymph nodes and appearance of new enlarged lymph nodes in the axilla after initial improvement on anti-tubercular therapy suggests a number of differential diagnoses: inadequate anti-tubercular treatment due to drug resistance or poor drug compliance, concomitant bacterial infection, and, rarely, re-activation of lupus activity.<sup>12</sup> Nonetheless, supervision of anti-tubercular therapy together with biochemical and microbiological testing excluded them all. The demonstration of acid-fast bacilli on direct smear but not from culture of the patient's axillary lymph node aspirate indicated that the acid-fast bacilli were not viable after 2 weeks of anti-tubercular treatment. This, together with the spontaneous resolution of lymphadenopathy while continuing anti-tubercular treatment, suggested a diagnosis of paradoxical deterioration. The surge in lymphocyte count during the time of apparent clinical deterioration further supported this diagnosis.

Paradoxical deterioration during anti-tubercular treatment is not uncommon. The prevalence of paradoxical deterioration among HIV-negative patients during treatment for tuberculosis has been recently reported at 11.1%.<sup>2</sup> Tuberculosis is also common among patients with chronic renal insufficiency,<sup>9-11</sup> but paradoxical deterioration has not previously been reported. It is possible that patients on dialysis are less prone to develop paradoxical responses: the host immune responses of such patients are altered and there is a high rate of anergy.<sup>13-15</sup>

The pathogenesis of paradoxical deterioration during anti-tubercular treatment remains to be fully elucidated. It may be related to the development of enhanced immunological responses against *M tuberculosis* during the course of anti-tubercular therapy.<sup>16,17</sup> In HIV-infected patients who develop paradoxical deterioration during anti-tubercular treatment after having received highly active antiretroviral therapy, clinical deterioration may be due to the immune reconstitution inflammatory syndrome, an exuberant inflammatory response towards the incubating *Mycobacterium*.<sup>18</sup> Corticosteroids have been prescribed to treat paradoxical deterioration.<sup>7</sup> Interestingly this offered no protection for the patient reported here. The dose was nonetheless small and might have been insufficient to entirely suppress the inflammatory response. The concomitant administration of isoniazid might also have reduced the effectiveness of the steroid.

There is no consensus on the optimal treatment for paradoxical deterioration during anti-tubercular treatment. The condition may be self-limiting as demonstrated by our patient. An expectant approach is probably called for with the continuation of anti-tubercular and pre-existing steroid therapy. Such an approach will also avoid the problem of side-effects associated with high-dose steroid therapy.

Paradoxical deterioration during anti-tubercular treatment can occur in CAPD patients on maintenance steroid therapy. Although self-limiting, clinicians should recognise this potential complication. In the absence of other causes of clinical deterioration, spontaneous resolution can be expected with no change required to any anti-tubercular or other concomitant pharmacotherapy.

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