

## Disseminated tuberculosis following immunosuppressive therapy for nephrotic syndrome

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### Introduction

Over 80% cases of nephrotic syndrome (NS) in children are due to minimal change disease and most respond to steroid therapy<sup>1</sup>. Steroid sensitive NS rarely progresses to end stage renal failure, over 80% entering spontaneous long term remission in later childhood<sup>2</sup>. In contrast, steroid resistant and refractory NS have an unfavourable outcome often progressing to end stage renal failure<sup>3,4</sup>. Infection is a universal concern in patients receiving cytotoxic or immunosuppressive therapy. Concomitant glucocorticoid therapy adds to this problem and the risk of infection with cytomegalovirus, *Pneumocystis carinii*, and varicella zoster is always present<sup>5</sup>. It is well known that severe attack of measles can re-activate tuberculosis<sup>6</sup> and this case report describes its reactivation following immunosuppressive therapy for NS.

### Case report

An eleven year old boy was referred to the Tertiary Care Nephrology Centre of the University of Peradeniya for further management of his initial episode of NS. He was treated with prednisolone 60mg/m<sup>2</sup>/day for 6 weeks but nephrotic range proteinuria (2.43mg/mmol) continued. He was oedematous, the serum albumin was 12g/L and he had a urine output of 0.3ml/kg/hour. He had persistent hypertension and with antihypertensive therapy his BP was 130/80 mmHg. His hepatitis B surface antigen and antinuclear antibody were negative and the complement assay was normal. He underwent

renal biopsy which revealed focal and segmental glomerulosclerosis. Hence he was commenced on 3 pulses of methyl prednisolone at 600mg/m<sup>2</sup> /daily and monthly pulses of intravenous cyclophosphamide at 600mg/m<sup>2</sup>.

Oral corticosteroid therapy was continued at 60mg/m<sup>2</sup> on alternate days for 4 weeks tapering 10mg/m<sup>2</sup> monthly. Oedema was initially controlled with the use of diuretics and after the second pulse of cyclophosphamide the child finally entered complete remission. After being in remission for 5 days, he was to be discharged after a prolonged hospital stay. However, on the day of discharge before leaving hospital he became unwell with cough and vomiting. He was commenced on intravenous fluids and the initial chest x-ray revealed opacities of the right lung with hilar lymphadenopathy (figure 1).



**Figure 1: Chest x-ray revealing opacities of right lung with hilar lymphadenopathy**

Thus he was commenced on intravenous cefuroxime. However, his clinical condition deteriorated rapidly and the chest X-ray done 24 hours later demonstrated complete opacification of the right lung. He was commenced on intravenous meropenem and received intensive care. His erythrocyte sedimentation rate was 133mm in the first hour and the polymerase chain reaction for *Mycobacterium tuberculosis* was positive in

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blood. The patient succumbed and the post-mortem examination revealed disseminated tuberculosis.

### Discussion

The activation of indolent TB during immunosuppressive therapy has received much emphasis in the western literature<sup>7,8</sup> but has always been a cause for concern in India. It is important to have a high degree of suspicion of the possibility of re-activation of TB during heavy immunosuppressive therapy especially in steroid resistant disease. Cytotoxic and immunosuppressive drugs while playing a pivotal role in induction and maintenance of remission in some types of NS in children, are themselves associated with significant morbidity. The risk of associated side effects is more pronounced in steroid resistant nephrotic syndrome (SRNS) and steroid dependent nephrotic syndrome (SDNS) where children are exposed to multiple courses of high-dose prednisolone. Glucocorticoids are known to strongly reduce the production of cytokines IL-1 $\beta$  and TNF- $\alpha$ , and many immunomodulatory cytokines such as IL-2, IL-10, IL-12 and IFN- $\gamma$  whereas cyclosporine and tacrolimus inhibit T cell function and IL-2 production<sup>9</sup>. TNF- $\alpha$  is a key cytokine in host defence mechanism against *Mycobacterium tuberculosis*<sup>10</sup>. Prolonged treatment with cytotoxic drugs such as cyclophosphamide and chlorambucil also places the patient at highly immunocompromised state. In a person with latent TB infection, such a shift in the immunological status can cause the *M. tuberculosis* bacteria to multiply further, resulting in disease which manifests as active TB<sup>11</sup>.

Given this proven increased risk of TB activation, screening patients for latent infection should take place before starting long-term immunosuppressive therapy. However currently a gold standard for such screening is lacking. The two main available tests are the tuberculin skin test (TST) and interferon- $\gamma$  release assays (IGRAs). Though TST shows high sensitivity in individuals with normal immune responses<sup>12</sup> the sensitivity in people with previous Bacille Calmette-Guérin (BCG) vaccination, prior exposure to nontuberculous mycobacteria and immunosuppressant medication is lower<sup>7</sup>. Though some studies suggest the T-SPOT blood test which is a type of IGRA to diagnose latent TB<sup>7,13</sup>, a study by Ratnatunga *et al* in Sri Lanka showed no advantage in using T-SPOT.TB over TST<sup>14</sup>. The TST is the most widely used method for TB

screening in these settings due to the significant advantage of low cost.

Despite the lack of a golden standard, the need for TB screening prior to heavy immunosuppressive therapy especially in children, remains important. Tuberculosis skin test, smear microscopy and chest radiography could be employed for this purpose, preferably after an individual risk assessment for each patient. It should also be taken into account that prophylactic therapy for TB carries a low risk of hepatotoxicity, which is also an undesirable side-effect of cyclophosphamide<sup>15</sup>.

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