A possible case of levamisole-induced pauci-immune focal necrotising and crescentic glomerulonephritis

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Background
Levamisole (LEV) has been used successfully in the management of nephrotic syndrome, various autoimmune disorders, and colon and breast cancers in humans[1-3]. It has been shown to reduce the relapse rate in frequently relapsing and steroid dependent nephrotic syndrome as a monotherapy[4] or with the combination of alternate day prednisolone[5-7]. Levamisole has the ability to act as a hapten. As suggested by recent literature, this might result in an altered immune response due to the increased formation of antibodies to various antigens[8]. Due to a number of cases reporting its adverse effects[9,10], especially LEV-induced vasculopathy[11,12], LEV was withdrawn from use in humans in the United States and Canada[13].

Drug-induced vasculitis is the most common form of vasculitis[14]. It may be difficult to differentiate between drug-induced and idiopathic vasculitic conditions. A way of distinguishing between these two conditions is withdrawal of the offending drug. Affected individuals usually present with cutaneous manifestations, arthralgia, leucopenia and positive anti-neutrophil cytoplasmic antibodies (ANCA) in high titres. A predilection for ear lobe involvement is seen. End-organ involvement however is a rare presentation of LEV induced vasculitis. Here we report a 12 year old girl who developed pauci-immune focal necrotising and crescentic glomerulonephritis following long term use of LEV.

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Case report
A 12 year old girl, a diagnosed patient with frequently relapsing steroid-sensitive nephrotic syndrome presented with a purpuric rash and nodules over upper and lower limbs. There was no arthralgia or arthritis. There were no urinary symptoms and she had a normal urine output. She had been on LEV (2.5mg/kg) on alternate days for two and half years and had a relapse free period of one year. Previous laboratory tests performed 3 months earlier revealed a creatinine level of 56µmol/l and an inactive urinary sediment.

On examination, she was pale but there was no oedema, lymphadenopathy or hepato-splenomegaly. Both upper and lower limbs revealed palpable purpura and a few skin nodules. Ear lobe involvement with purpura was also seen. The rest of the systemic examination was clinically unremarkable except for a marginally elevated blood pressure of 134/72 mmHg. Her urine dipstick showed 2+ protein and microscopic haematuria. Urine albumin/creatinine ratio was 156 mmol/mg. Laboratory testing showed a white blood cell (WBC) count of 3600 per cu mm (normal range of 4000-11000 per cu mm), a haemoglobin level of 7.8 g/dl and a platelet count of 127,000 per cu mm (normal range of 150,000-400,000 per cu mm). Erythrocyte sedimentation rate was 110 mm in first hour and renal function revealed serum creatinine of 88µmol/l.

Anti-neutrophil cytoplasm antibodies (ANCA) were positive in high titres. Anti-nuclear antibodies and double standard DNA antibodies were negative. Normal complement C3 and C4 levels were observed. An ultrasound scan showed slightly enlarged kidneys and no other remarkable findings. She underwent both renal and bone marrow biopsies. Bone marrow biopsy findings were not in favour of malignancy or aplasia. Pathological findings of the renal biopsy were consistent with pauci-immune focal necrotising and crescentic glomerulonephritis (Figure 1 and 2).

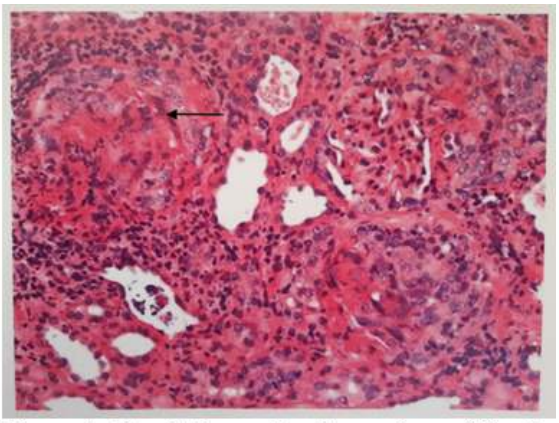

Figure 1: ***Renal biopsy showing regions of focal necrotizing glomerulonephritis***

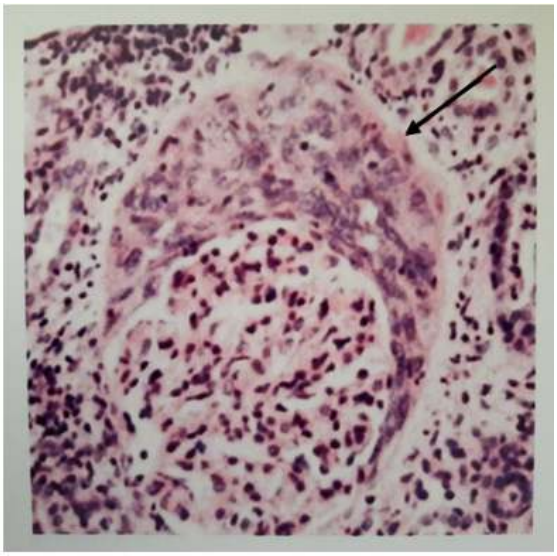

Figure 2 Renal biopsy showing crescent formation

LEV was stopped on admission. The patient received 3 doses of methyl prednisolone at 600mg/m^2 on consecutive days followed by the first dose of intravenous cyclophosphamide. She was then commenced on oral prednisolone at 60mg/m^{2}daily for 4 weeks and a further two doses of intravenous cyclophosphamide were given at monthly intervals.

One month after the commencement of treatment, the urine albumin/creatinine ratio improved to 44 mg/mmol and prednisolone was reduced to a 40 mg/m^2 alternate day regime. All three cell lines showed improvement after two weeks of stopping LEV. At the three month follow-up, urine albumin/creatinine ratio was normal, renal functions revealed serum creatinine of 62µmol/l and titres of ANCA came down significantly. Tapering off of prednisolone is ongoing to maintain remission in NS.

Discussion

Levamisole is an anthelmintic drug with immunomodulatory properties. It has been successfully used in a dose of 2.5mg/kg every other day, alone or in conjunction with every other day prednisolone for frequently relapsing nephrotic syndrome and steroid dependent nephrotic syndrome. Its steroid-sparing effect combined with minimal side effects is the main advantage of LEV. There is accumulating evidence to suggest that LEV remains an attractive alternative which could contribute towards a reduction of the maintenance dose of corticosteroids and prolongation of the period of remission[5-7, 15-17]. However, LEV has not received approval for this indication in Europe. While difficulty in acquiring this drug may be one reason, the lack of sufficient evidence for its effectiveness could be another. In contrast, in the Asian subcontinent LEV is being used widely.

There are several case reports of LEV induced vasculopathy following use of LEV–adulterated cocaine in Europe and USA. Patients commonly presented with purpuric skin rash or bullae with ear involvement, arthralgia, leucopenia and positive ANCA in high titres. However, renal and pulmonary involvement are rarely seen in LEV-induced vasculitis. In a study by McGrath *et al*[18] on 30 patients with ANCA positivity associated with LEV contaminated cocaine use, 8 patients showed abnormal urinalysis at diagnosis. Of the two patients who developed severe acute kidney injury, one had a renal biopsy which revealed pauci-immune focal necrotising and crescentic glomerulonephritis. Both these patients ultimately had chronic kidney disease, although their renal functions improved with immunosuppressive treatment.

Cutaneous vasculitis is known to occur in patients having prolonged treatment with LEV, as opposed to the minority who develop a systemic drug-induced syndrome[19]. It usually affects the skin and sometimes the subcutaneous part of the skin[20], but sometimes also the kidney and the lungs[21]. If LEV is withdrawn early, there is usually complete recovery whilst if LEV is withdrawn late, immunosuppressive therapy may be needed[14]. Patients with drug induced vasculitis typically harbour ANCA directed to one or more neutrophil cytoplasm antigens and it seems that ANCA appeared in the blood sometimes before the clinical manifestations.

In our case, the child had been on LEV (2.5mg/kg) on alternate days for two and a half years. Even though she had been monitored with regular full blood counts, ANCA in serum was not performed. We have seen a remarkable improvement of her skin manifestations and cell line indices soon after

withdrawing LEV. After 3 months of immunosuppressive therapy, urine albumin/ creatinine ratio had become normal and renal functions returned to the baseline. These findings indicate that immunosuppressive therapy could be given for a shorter time than in primary ANCA-associated vasculitis and long term maintenance therapy may not be needed.

One could argue that this was a case of idiopathic pauci-immune vasculitis which responded to the immunosuppression. We believe that the ear lobe involvement at the onset and the rapid response to discontinuation of levamisole are in favour of levamisole induced pauci-immune vasculitis with necrotising and crescentic glomerulonephritis. End organ involvement is a rare presentation of ANCA positive vasculitis induced by LEV.

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