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Extracapillary glomerulonephritis during etanercept treatment for juvenile psoriatic arthritis

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ABSTRACT

Juvenile psoriatic arthritis was diagnosed in a girl of 15 and a half years old, who presented with severe polyarthritis and psoriasis. Treatment with etanercept 25mg by subcutaneous injections, twice a week was started. After 5 months of treatment, she developed microscopic hematuria, proteinuria and progressive acute renal failure with anaemia and hypertension. Renal histology, IF, and EM findings were consistent with severe extracapillary crescentic pauciimmune glomerulonephritis. The histology findings, the onset of renal symptoms after beginning treatment with etanercept, and the absence of any abnormality in the urine tests before administration of the drug, support the hypothesis of a rare case of secondary nephropathy due to treatment with an anti-TNF-α drug.

Introduction

Anti-TNF-α agents are widely used, even in paediatric patients, for the treatment of various rheumatic and autoimmune disorders (juvenile idiopathic arthritis, psoriatic arthritis, spondyloarthropathy, severe vasculitis, juvenile dermatomyositis, auto-inflammatory syndromes, etc.) (1, 2). Etanercept is a combination of two naturally occurring soluble human 75-kilodalton TNF receptors linked to the Fc portion of an IgG1. This artificially engineered dimeric fusion protein acts as a "decoy" circulating receptor for TNF-α (3). Extensive use of this class of agents has led to recognition of novel significant side effects. Hematological or cardiac disorders have been reported, as well as disturbances at the level of the central nervous system (4). Other observations include induction of autoantibodies (ANA, anti-dsDNA, anti-cardiolipin antibodies) (5) and the occurrence of a reversible lupus-like syndrome in subjects treated with anti-TNF-α for rheumatoid arthritis (6, 7). On the other hand, renal complications have been very rare (8, 9), and none of the cases reported concerned patients in paediatric age.

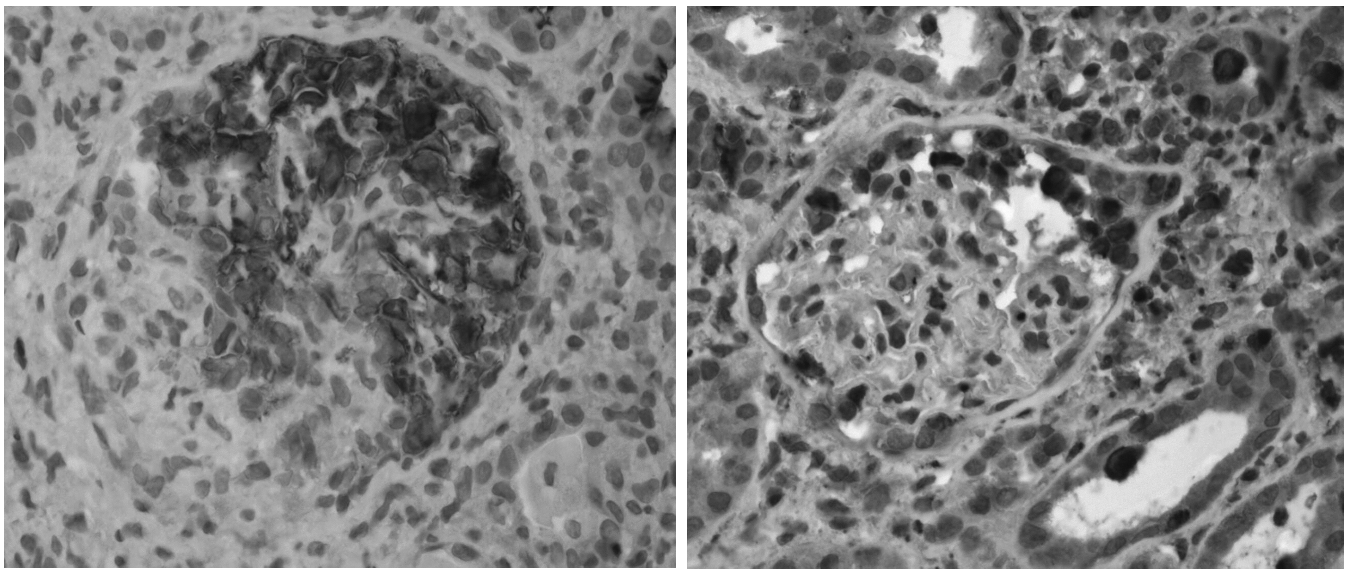
We herein describe the case of a 16-year-old girl who developed glomerulonephritis during the course of therapy with etanercept for psoriatic arthritis.

Clinical case

A 15 and a half year-old girl presenting with simultaneously polyarthritis and psoriasis had a familial and personal history negative for autoimmunity. She was diagnosed with juvenile psoriatic arthritis (10), which was first treated with naproxen and methotrexate. After 5 months, due to persistence of the symptoms, she started etanercept 25 mg by subcutaneous injections, twice a week. Naproxen and methotrexate were withdrawn. At the start of etanercept, urinary analysis and renal function were normal. Five months into treatment, microscopic hematuria with dysmorphic erythrocytes, proteinuria and hyaline-granular cylinders were noted at urinalysis. Proteinuria, which initially was 0.98 gr/day, gradually increased within 1 month to 1.7 gr/day. Serum creatinine increased from 1.10 mg/dl to 2.4 mg/dl, and the glomerular filtration rate calculated according to Cockroft and Gault decreased from 71.4 ml/min/m^2 to 43 ml/min/m^2. Progressive anaemia was also present (initially RBC 3,500,000/μ^3, Hb 9.2 g/dl, Ht 28%, later decreasing to 2,900,000/μ^3, Hb 7.3 g/dl, Ht 24%). ANA, n-DNA, ENA, c-ANCA, p-ANCA, and Rheumatoid Factor (RF) were negative, thus ruling out a systemic vasculitis. Serum complement levels (both C_3 and C_4) were within normal parameters. Blood pressure was on average 145/90 mmHg. Clinical symptoms of vasculitis were absent.

A renal biopsy was then performed. Specimen containing 29 globally enlarged glomeruli, 23 of which (80%) partially obliterated by cellular crescents (Fig. 1 A). About 50% of cells in the crescents were CD68+ macrophages/monocytes (Fig. 1 B). In 2 glomeruli focal segmental necrosis was noted next to areas of intracapillary thrombosis. No polymorphonuclear cell infiltrates were seen within glomeruli, while abundant lymphomononuclear cells were present within tubulointerstitial areas and surrounding selected glomeruli (Fig. 2). IF was negative for IgG, IgM, IgA, κ and λ light chains, C3, C4, C1q, while a faint positive fluorescence for fibrinogen was detectable in 8 of 10 glomeruli.

Electron microscopy (EM) showed mild mesangial proliferation with segmental



A B

Fig. 1. Cellular crescent resulting from infiltrating, CD10-negative cells. Immunoperoxidase, original magnification 250x.
Panel **A**: note clustering of intrinsic CD-10 positive glomerular cells towards the upper right pole of the glomerulus. CD10 selectively stains podocytes and parietal epithelial cells. Panel **B**: CD68-positive monocyte/macrophages account for a majority of the cells in the crescents.

splitting and reduplication of glomerular basement membranes (GBM) by mesangial processes. Podocytes were enlarged with diffuse foot process effacement. Occasional intramembranous electrondense deposits, but no subepithelial or subendothelial deposits, were noted. Marked pericapillary and pericapsular monuclear cell infiltrates in a majority of glomeruli. Renal histology, IF, and EM findings were consistent with severe extracapillary crescentic pauciimmune glomerulonephritis.

In the belief that etanercept (the only drug administered to the patient) may have triggered the glomerulopathy, treatment was interrupted, and three consecutive pulses of methylprednisolone (1 gr/day) were then administered, followed by maintenance therapy with prednisone – 1 mg/kg/day for 6 months. Within a month, renal function returned to normal. No cytotoxic agents were administered, based on severe anemia, the absence of other systemic signs of vasculitis, and negativity of renal IF. Steroids were gradually tapered off within further 45 days.

At 18 months, serum creatinine is stable at 0.8 mg/dl, creatinine clearance 103 ml/min, BUN 23 mg/dl, while proteinuria persists and is still around 1.5–2.4 g/24 hrs. Anemia was rapidly corrected after 1-month supplementation with oral iron, folic acid and vitamin B12, with RBC persisting at 4,470,000/mm^3 and Hb of 12.2 g/dl at 18 months. No further psoriasis manifestations or rheumatologic signs were reported at follow-up, with negativity of RF.

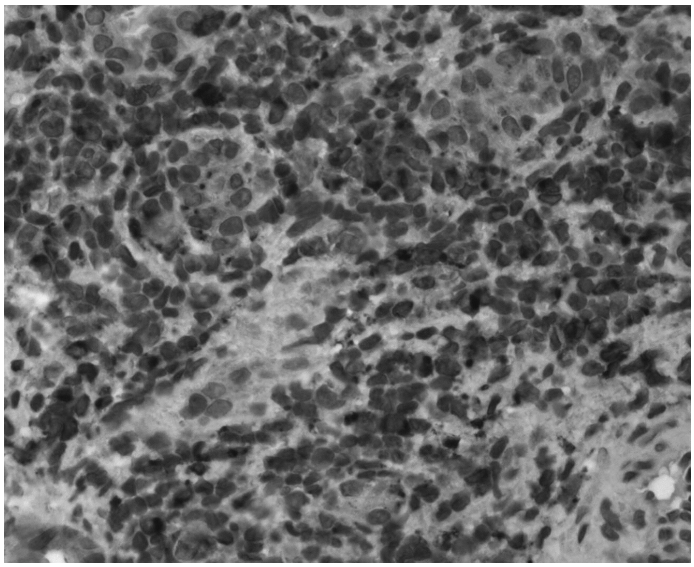


Fig. 2. Marked CD68-positive tubulo-interstitial infiltration; immunoperoxidase, original magnification 250x.

Discussion

Recently, reports have appeared on cases of glomerulonephritis in patients treated with anti-TNF-α drugs (11-14). Histological examination of renal biopsies yielded multiple type of lesions: membranous glomerulopathy, pauciimmune necrotising glomerulonephritis with crescents, and lupus nephritis. The possible involvment of anti-TNF-α drugs in the genesis of renal damage in these patients has been hypothesised by the following considerations: (i) the time elapsed between administration of the drug and the onset of renal symptomatology, (ii) the absence of previous renal symptoms or signs, (iii) the resolution of renal symptomatology after discontinuing therapy replaced by steroids and immunosuppressant drugs, and (iv) the death of a single patient whose therapy had not been suspended.

In our case, kidney involvement could not be attributed to a complication of the background disease, such is often the case with amyloidosis, since only a short time had elapsed from the onset of articular inflammatory symptoms (only 18 months). Most importantly, histological examination of the renal biopsy did not show any amyloid deposits. A classical "rheumatoid nephropathy" was ruled out by the renal biopsy, which did not show patterns of mesangial glomerulonephritis, minimal lesion glomerulopathy or p- / c-ANCA positive necrotising glomerulonephritis. A lupus nephritis in a patient suffering from psoriatic arthritis during an overlap syndrome or a mixed-connective tissue disease was also considered (15), but negative ANA, n-DNAs and ENAs, normal C3 and C4 serum complement levels, and the results obtained from the renal biopsy were not consistent with this hypothesis.

Therefore, the one possible interpretation of the histology findings was a secondary glomerulopathy due to treatment with an anti-TNF-α drug. Supporting this hypothesis was the onset of renal symptoms some 5 months after beginning treatment with etanercept (the only agent used in this patient), the absence of any alterations in the urine test before starting the drug, and reports in literature of some cases of etanercept-induced, or -aggravated preexisting glomerulopathy. Two of these reports describes three cases with a renal histological picture similar to ours (8, 11). Nevertheless, rare cases of extracapillary, rapidly progressive glomerulonephritis observed during RA should raise a note of caution on a possible link with the initial rheumatologic disorder in this patient (16).

Knowledge of the potential adverse effects of anti-TNF-α agents should not, however, limit the use of these drugs, which have literally overturned the natural history of many diseases. Rather, it should lead to monitoring of autoantibodies and renal function, both before and during treatment. Early identification of a possible autoimmune disorder secondary to the use of etanercept would lead to the only effective approach, that is, withdrawal of the offending drug.

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