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BRIEF REPORT

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Tubulointerstitial nephritis and uveitis in association with Epstein-Barr virus infection

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Abstract The case of a 13.5-year-old girl with acute tubulointerstitial nephritis and uveitis (TINU syndrome) is presented. The etiology of this rare syndrome, which in most cases involves female adolescents and usually regresses spontaneously, is still unknown. An infection-triggered pathological immune reaction has been considered to play a role in the pathogenesis of this disorder. Here we report for the first time the association of TINU syndrome and Epstein-Barr virus infection.

Key words Interstitial nephritis · Uveitis · Epstein-Barr virus · Corticosteroids · TINU syndrome

Introduction

Since the first description of TINU (*t*ubulo*i*nterstitial *n*ephritis and *u*veitis) syndrome in 1974, more than 50 cases have appeared in the literature. Although some reports have suggested that an infection-triggered pathological immune reaction plays a role in the pathogenesis of this disorder [1, 2], the etiology and pathogenesis of this syndrome are still unknown. To date, an association of TINU and Epstein-Barr virus (EBV) infection has not been reported.

Case report

A 13.5-year-old daughter of a German mother and an Afro-American father was admitted to our hospital in April 1997 because of proteinuria, glucosuria, and acute renal dysfunction. Three months prior to admission, the patient had a 2-week period of lymphadenopathy and fever. Acute EBV infection with characteristic atypical lymphocytosis and positive EBV VCA IgG and IgM titers was diagnosed. Over the next 3 months, she suffered from elevated temperatures up to 38.5°C, malaise, pallor, and fatigue. During that time the girl lost approximately 20 kg of weight. The swelling of the lymph nodes subsided rapidly. However, the patient's erythrocyte sedimentation rate (ESR) (>100 mm/h) and, to a lesser extent, the C-reactive protein (CRP) (15 mg/l) remained elevated and anemia persisted (hemoglobin 10 g/dl). She presented to our hospital complaining of pain and redness of the left eye, photophobia, and exhaustion. There was no history for nocturia, polydipsia, or polyuria.

On admission, the girl was still markedly overweight (95.5 kg, 161.6 cm, body mass index 36.8 kg/m^2). Blood pressure was 140/90 mmHg. The eye showed ciliary injection and anterior uveitis was diagnosed. Except for generalized signs of atopic dermatitis, complete physical examination was otherwise unremarkable. Hemoglobin was 10.9 g/dl, white blood cell count was 8,500/mm^3 with 72% neutrophils, 1% basophils, 25% lymphocytes, and 2% monocytes. Serum creatinine was increased to 139 µmol/l and creatinine clearance was decreased to 52.6 ml/min per 1.73 m^2; blood urea nitrogen and uric acid, as well as serum sodium, potassium, and phosphate were normal. Urinalysis showed a pH of 6.0, mild proteinuria (30 mg/dl) of tubular origin, and glucosuria (100 mg/dl). Aminoaciduria was not present. Leukocytes and erythrocytes were not detected in urine.

Further laboratory examination revealed an elevated ESR (114 mm/h), an elevated CRP (15 mg/l), and pathologically elevated plasma concentrations of total protein [96.6 g/l (normal <80 g/l)], IgA [514 mg/dl (normal 40–240 mg/dl)], IgM [267 mg/dl (normal 50–220 mg/dl)], IgG [2,110 mg/dl (normal 700–1800 mg/dl)], and IgE [3,335 U/l (normal <100 U/l)]. Circulating immune complexes (CIC) were elevated: [IgG–CIC 15 mg/dl (normal <9 mg/dl), IgM-CIC 42 mg/dl (normal <20 mg/dl)]. Plasma concentrations of complement components, C3c and C4 were 1,480 mg/l (normal 520–1,200 mg/l) and 906 mg/l (normal 205–490 mg/l), respectively. LE cells, anti nuclear, anticytoplasmic, and anti-DNA antibodies were not detectable. Serum rheumatoid factor was negative. Positive titers were found for anti-streptolysin O (400 IU/ml), anti-streptodornase (800 IU/ml), and antistaphylosin antibodies (2 IU/ml).

Serological testing for EBV showed negative EA-IgG, positive EA-IgM (0.4) and positive EBNA-I (2.7) titers, compatible with a recent infection. Serological testing for chlamydia, hepatitis A, B, and C, human immunodeficiency virus, *Treponema pallidum*, *Borrelia*, cytomegalovirus, toxoplasma, herpes simplex, rubella, influenza, parainfluenza, adeno virus, and parvo virus B19 was negative. Bone marrow examination revealed no granulomatous lesions. Chest X-ray, ultrasound examination of the abdomen, electrocardiography, echocardiography, and renal scintigraphy were normal.

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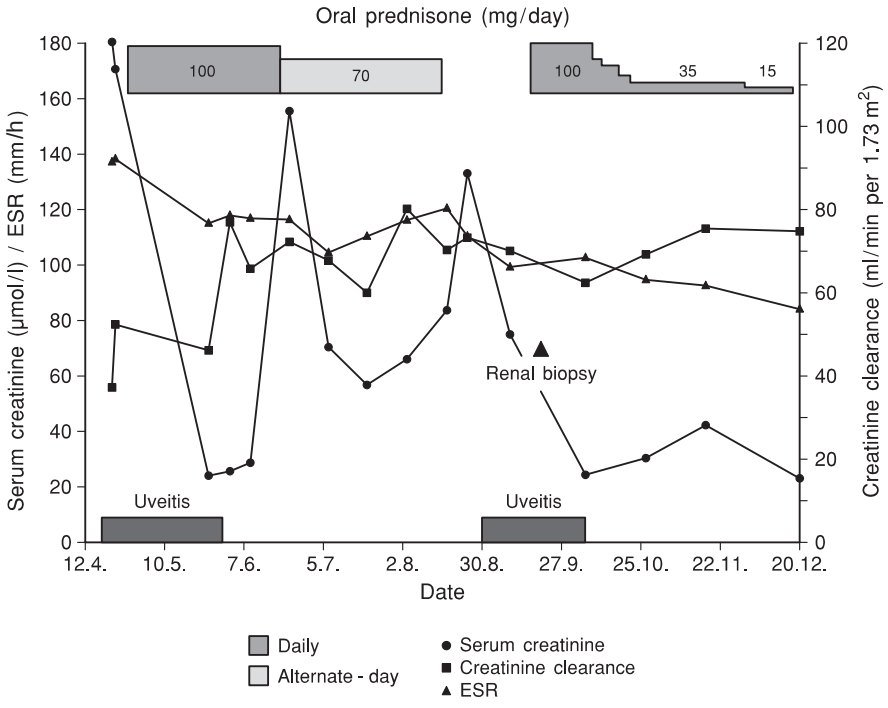

Fig. 1 Course of serum creatinine, creatinine clearance, and eythrocyte sedimentation rate (*ESR*) over a period of 8 months

After excluding rheumatoid and other systemic diseases, TINU syndrome was suspected. Systemic prednisone treatment (60 mg/m^2 per day) was started. Clinical and laboratory signs of nephritis improved rapidly on this regimen (Fig. 1). However, despite additional treatment of the uveitis with topical corticosteroids and mydriatics, posterior synechia of the left eye developed.

After discontinuation of the prednisone therapy after 2.5 months, uveitis relapsed within 3 weeks. Renal function worsened again, with creatinine clearance decreasing to around 60 ml/min per 1.73 m^2. There was no return of glucosuria, while mild proteinuria recurred. The ESR was rising to pathological values. At that point, a renal biopsy was performed (Fig. 2), showing a normal glomerular and arterial architecture with no signs of vasculitis, narrow tubuli, along with a thickening of the basal membranes, focal necrosis, and atrophy of tubular epithelia, together with signs of interstitial cellular infiltration and interstitial fibrosis. The mononuclear infiltration mainly consited of CD3-positive lymphocytes, with some CD8-positive T cells and no CD4-positive cells. These findings are in accordance with the diagnosis of tubulointerstitial nephritis. Therefore, prednisone therapy was reintroduced. After rapid improvement of clinical and laboratory signs of both nephritis and uveitis, prednisone was tapered over a period of 3.5 months to 15 mg/day without a new flare-up.

Discussion

In 1974, Guignard and Torrado [3] first described the coexistence of tubulointerstitial nephritis and uveitis in a girl with toxoplasmosis. In 1975, Dobrin et al. [4] reported two adolescent females with acute eosinophilic interstitial nephritis and renal failure with bone marrow and lymph node granulomas and anterior uveitis. After the publication of numerous other case reports, Vanhaesebrouck et al. [5] introduced the acronym TINU in 1985 for *t*ubulo*i*nterstitial *n*ephritis plus *u*veitis. Since that time, more than 50 cases have been reported. This rare disease most commonly occurs in adolescent girls; among the 36 cases of 10- to 18-year-old patients reported to 1996, 13 were male, while 23 were female [6].

In most cases, the beginning of the disease is uncharacteristic. The predominant symptoms are fever, easy fatiguability, loss of appetite, and weight loss. Usually this phase is followed by renal symptoms of acute nonoliguric renal dysfunction. Sterile leukocyturia, glucosuria, and predominantly tubular proteinuria may also be observed [1]. Laboratory examinations usually show a markedly elevated ESR, an increase of gamma globulin concentrations, and anemia [7].

Usually, uveitis manifests within weeks to months of the beginning of the nephritis [7], but it may also precede the renal symptoms [8]. In most cases, bilateral anterior uveitis is observed. This can lead to synechiae, which may cause intraocular hypertension and retinal bleeding [1].

Both renal dysfunction and uveitis usually regress spontaneously [4, 7] or upon systemic treatment with steroids [1, 8]. Ocular symptoms have also been described to respond well to topical steroid therapy. Uveitis tends to relapse frequently, in many cases despite an improvement of the nephropathy [8].

Clinical symptoms, laboratory results, and the course of the disease, including the response to prednisone treatment, unequivocally allow the diagnosis of TINU syndrome in our patient.

The etiology of this ocular-renal disorder has remained unclear. Immunological mechanisms have repeatedly been discussed. It has been assumed that an exaggerated T cell-mediated immune response is involved. This is supported by reports of a decreased CD4/CD8 ratio, an increased expression of CD25, the low-affinity receptor for interleukin-2 on T lymphocytes, and higher

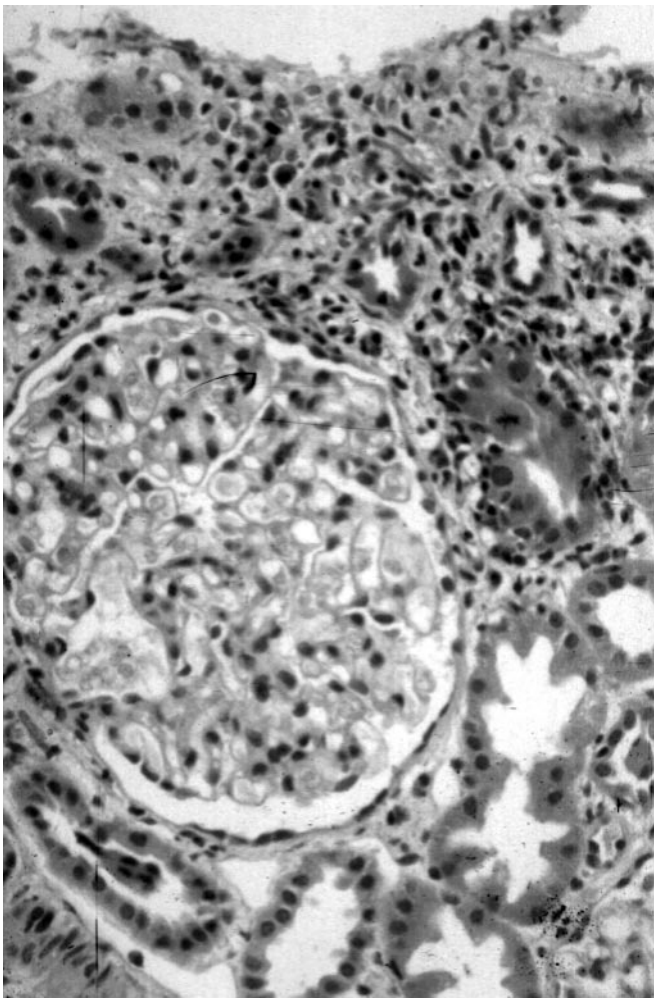

Fig. 2 Renal cortex with normal glomerulus and T cell-rich interstitial inflammation, tubular atrophy and some CD-8 positive T cells associated with tubular epithelium (CD8, DAKO, ×35)

circulating levels of soluble tumor necrosis factor receptor during the active stage of the disease. The possibility of a suppression of cellular immunity has also been suggested. Gafter et al. [9] demonstrated that T cell function in vitro as well as in vivo is decreased during remission of TINU syndrome. The elevated immunoglobulin levels detected in our patient, as well as those from the literature, also point to an involvement of B lymphocytes.

Tubulointerstitial nephritis may be caused by drugs, infectious agents, and immunological disorders. In our case we could not find any signs suggestive for classic autoimmune diseases such as systemic lupus erythematosus, sarcoidosis, or Behçet syndrome. There was no history of drug treatment, particularly of non-steroidal anti-inflammatory drugs, which are known to predispose to interstitial nephritis [10].

An infectious agent triggering the development of TINU syndrome could not be found in most of the cases in the literature, although there have been reports of the association of TINU syndrome and toxoplasmosis [3] and TINU syndrome and chlamydial infection [11]. Here we report for the first time an association of TINU syndrome and EBV infection.

Renal complications in EBV infection are rarely seen [12], although as early as 1967 interstitial nephritis was described in patients with infectious mononucleosis (IM). Acute lymphocytic or lymphomonocytic infiltration, however, seem to occur frequently in clinically inapparent renal involvement of EBV infection. Post mortem studies of 30 fatal cases of IM led to the observation that lymphocytic infiltration of most organs is usual, and that the degree of organ dysfunction is directly related to lymphocytic infiltration [13]. Thus, lymphocytic infiltration seems to be the main pathogenetic mechanism in the rare cases of acute renal failure in IM [12]. Various efforts to demonstrate the presence of EBV genetic material in renal tissue were unsuccessful [13]. It is known, however, that T lymphocytes do not bear receptors for EBV, and the virus has never been detected in epithelia composed of a monolayer of cells [13].

Ocular involvement in acute EBV infection is usually limited to a transient follicular conjunctivitis [2], although a few cases of more-severe ophthalmic complications of chronic EBV infection have been reported in the literature. In most of these cases bilateral anterior uveitis has been observed which responded well to topical steroid therapy [2, 14].

To date there have been no reports of the coexistence of TINU and EBV infection. EBV with its known effects on T and B cells is an attractive candidate to play a role in this rare syndrome, and we suggest systematic monitoring for EBV in cases of TINU syndrome.

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LITERATURE ABSTRACT

G. Klaus · L. Weber · J. Rodríguez · P. Fernández · T. Klein J. Grulich-Henn · U. Hügel · E. Ritz · O. Mehls

Interaction of IGF-I and 1 alpha, 25(OH)2D3 on receptor expression and growth stimulation in rat growth plate chondrocytes

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Growth plate cartilage cells express receptors for, and are affected by both IGF-I and 1 alpha, 25(OH)2D3. The studies were undertaken to investigate interaction between these two hormone systems, that is, (i) to study effects of 1 alpha, 25(OH)2D3 on IGF-type 1 receptors (IGFIR), on IGF-I stimulated cell replication, colony formation, and on alkaline phosphatase activity (AP), and conversely, (ii) to study the effect of IGF-I on vitamin D receptor (VDR) expression on 1 alpha, 25(OH)2D3 stimulated growth parameters and on AP activity. Freshly isolated rat tibial chondrocytes were grown in monolayer cultures, (serum-free) or in agarose stabilized suspension cultures (0.1% FCS). Vitamin D receptor and IGFIR were visualized by immunostaining with the monoclonal antibody (mAb) 9A7 gamma and mAb alpha IR3, respectively, and quantitated by RT-PCR for mRNA and by Scatchard analysis using [3H]-1,25(OH)2D3 and [1,25I]-alpha IR3. Cell proliferation was measured by [3H]-thymidine incorporation, growth curves in monolayer cultures, and by colony formation in agarose-stabilized suspension cultures. IGF-I dose-dependently increased [3H]-thymidine incorporation. 1 alpha, 25(OH)2D3, but not 1 beta, 25(OH)2D3 was stimulatory at low (10–12 M) and slightly inhibitory at high (10–8 M) concentrations. The effect of IGF-I was additive to that of 1 alpha, 25(OH)2D3[IGF-I 60 ng/ml, 181+/–12.7; 1 alpha, 25(OH)2D3 10(–12) M, 181+/–9.8%, IGF-I+1 alpha, 25(OH)2D3, 247+/–16.7%, $P<0.05$ by ANOVA and specifically obliterated by polyclonal IGF-I antibody (AB-1). Interaction could also be confirmed in suspension cultures. IGFIR mRNA and [125I]-alphaR3 binding was increased by low (10(–12) m) but not by high (10(–8) M) concentrations of 1 alpha, 25(OH)2D3. Homologous up-regulation by IGF-I (60 ng/ml) was specifically inhibited by AB-1 and markedly amplified by coincubation with 1 alpha, 25(OH)2D3 (10(–12) m). Immunostaining with alpha IR3 showed specific IGFIR expression in rat growth cartilage, but not liver tissue. Stimulation of chondrocytes with 1 alpha, 25(OH)2D3 or IGF-I suggested some increase of receptor expression in single cells, but the predominant effect was increased recruitment of receptor positive cells, Vitamin D receptor expression was markedly stimulated (fourfold) by IGF-I (60 ng/ml), but not IGF-II and inhibited by actinomycin D. This study shows that IGF-I and 1 alpha, 25(OH)2D3 mutually up-regulate their respective receptors in growth plate chondrocytes. In parallel, they have additive effects on cell proliferation and colony formation suggesting independent effector pathways.