Introduction

Acute interstitial nephritis (AIN) has been described in association with infection, drug reactions, and disorders of immunity [1,2]. On the other hand, granuloma formation and uveitis is known to occur in a variety of systemic diseases. AIN is not commonly associated with uveitis, but the concomitant development of these disorders raises the concept of a renal–ocular syndrome. In 1975, Dobrin et al. [3] described a new syndrome consisting of acute renal failure (ARF) secondary to AIN associated with lymph node and bone marrow granulomas and anterior uveitis. The presence of renal granulomas had been demonstrated in only three previous cases. We describe one patient with AIN and renal granulomas associated with uveitis, compatible with those of the syndrome described by Dobrin et al. [3]. However, our case presents an aspect of special interest: the development of acute deafness followed by dramatic improvement under systemic corticosteroid therapy, suggesting an immunological involvement in its pathogenesis. This association has not been previously reported, and it may represent a new form of the original syndrome reported by Dobrin et al. [3].

Case report

A 15-year-old boy was referred to our hospital for renal insufficiency. He had been well until December 1994 when he developed a febrile illness associated with slight cough, malaise, weakness and headache. A few days later his eyes became red and he complained of discomfort and photophobia. This episode was diagnosed as conjunctivitis. Despite an initial improvement with local antibiotic eye drops, he continued complaining of itching redness, and bilateral eye pain. Ophthalmological consultation documented the presence of bilateral anterior uveitis. The inflammatory reaction and all ocular symptoms resolved with topical treatment of dexamethasone and atropine 1%. On initial examination by the family physician, his creatinine and blood urea nitrogen (BUN) levels were 2.1 mg/dl (186 μmol/l) and 42 mg/dl (15 mmol/l) respectively, and he was referred to our hospital.

On admission the patient was afebrile and his blood pressure was 110/70 mmHg. The clinical examination was normal. The patient had no preceding history of skin rash, arthralgias, drug abuse, ingestion or exposure to toxic agents, and he denied the use of analgesics other than paracetamol, antibiotics, or other drugs. Initial laboratory studies showed: haemoglobin 123 g/dl; white blood cell count 7560/mm³, with 51% polymorphonuclear leukocytes, 31.5% lymphocytes, and 4.8% eosinophils. The erythrocyte sedimentation rate (ESR) was 80 mm/h (Westergren). Serum creatinine was 1.7 mg/dl (159 μmol/l) and BUN 36 mg/dl (13 mmol/l). Serum electrolytes, blood iron, urate, and hepatic tests were normal. Total serum protein, albumin, complement and immunoglobulins were normal, except for increased IgG (1980 mg/dl, normal 720–1650). Antinuclear antibodies, anti-double-stranded DNA, antineutrophil cytoplasmic antibodies (ANCA), and rheumatoid factor test were negative. Urine examination revealed 1013 specific gravity, 8–10 leukocytes and 0–2 erythrocytes per high-power microscopic field, with no casts. The 24-h urine protein excretion, glucosuria and aminoaciduria were negative. Serological results for Epstein–Barr virus, cytomegalovirus, herpes simplex virus, hepatitis B, C, and human immunodeficiency virus, and a tuberculin test were negative. Cold agglutination, brucella agglutination and tests for toxoplasma and syphilis were also negative. The antistreptolysin O titer (ASO) was normal. Serial blood and urine cultures showed no growth. Results of the chest X-ray and abdominal ultrasound examination were normal.

During hospitalization anterior uveitis relapsed. A new ophthalmological examination showed normal visual acuity. No conjunctival nodules or lacrimal gland enlargement were found. Intraocular pressure, tear formation as judged by Schirmer’s test, lenses, and fundi were normal. Ocular alterations resolved by topical corticosteroid eyedrops.

A percutaneous renal biopsy revealed a heterogen-
euous interstitial cellular infiltrate composed of monocytes, lymphocytes, and plasma cells, with small non-caseating granulomas formed by epitheloid cells and multinucleated giant cells (Langhan’s type) (Figures 1 and 2). The tubular epithelial cells showed signs of degeneration, patchy necrosis, and regeneration. The vessels and glomeruli were unremarkable. Immunofluorescence was negative for fibrinogen, immunoglobulins, and complement components on glomerular as well as on tubular structures.

Oral prednisone treatment (1 mg/kg/day) was begun following the renal biopsy. Steroids were gradually tapered and then discontinued. Serum creatinine decreased within 1 month to 0.7 mg/dl (66 μmol/l). Three weeks after the end of steroids the patient developed a right sudden deafness, and laboratory tests revealed an increase in serum creatinine concentration to 1.5 mg/dl (141 μmol/l). His audiogram demonstrated a sensorineural deafness (Figure 3A). Magnetic resonance imaging of the brain was normal.

Oral prednisone was reinitiated (1 mg/kg/day). The patient’s hearing significantly improved after 10 days and returned to normal within 3 weeks, as confirmed by repeat audiogram (Figure 3B). Renal function improved with a decrease in serum creatinine to basal values. Six months after the onset of deafness he is well, with normal hearing and normal renal function, receiving no therapy. The clinical course of the patient is shown in Figure 4.

**Discussion**

Interstitial nephritis may be caused by drugs, toxins, infectious agents, or systemic diseases [1–3]. Our patient had a febrile illness associated with ARF, and in whom the renal biopsy demonstrated an AIN with granulomas. Numerous drugs may cause AIN, but the most common are non-steroidal anti-inflammatory drugs and beta-lactam antibiotics. The patient had received paracetamol, but this drug has been rarely related to AIN. Furthermore, although granulomas are not unusual in drug-induced AIN, they regress less completely and less rapidly than non-granulomatous cell infiltrates, and thus engender the risk of renal sequelae, which was not the case in our patient. In addition, our patient did not have joint pain, rash, peripheral eosinophilia, elevated IgE levels, or other symptoms usually associated with a drug-related disease. On the other hand, our investigations failed to reveal evidence in support of other processes such as eosinophilic syndromes, vasculitides, collagen–vascular disorders, or sarcoidosis [4].

Uveitis may occur in a wide variety of systemic disorders, including infections, sarcoidosis, Reiter’s and Behçet’s syndrome, and others characterized by granulomas, but our patient had neither the history, nor the physical and laboratory findings compatible with these diseases. Uveitis is very rarely associated with AIN. This association in patients in whom these possible causes had been excluded has therefore been called idiopathic AIN associated with uveitis [5], renal–ocular syndrome [1] or tubulointerstitial nephritis and uveitis (TINU syndrome) [6]. Our patient showed ARF secondary to AIN with renal interstitial granulomas, associated with anterior uveitis.

In 1975, Dobrin et al. [3] described two patients who suffered from AIN with granulomas and anterior uveitis of unknown cause, and considered it as a new syndrome. Since then more than 50 cases of AIN and uveitis have been published, some of them without bone marrow or lymph node granulomas [7,8]. However, the presence of renal granulomas has been rarely reported [3,9,10]. The aetiology and the pathogenesis of this syndrome remain unknown. In several cases some disturbances, such as elevation of the ESR, raised levels of immunoglobulins, and circulating complexes have been noted [6,10]. Recent studies have demonstrated that activated memory T cells represent the majority of the cells infiltrating the renal interstitium [8]. Other authors have reported immunological abnormalities such as decreases in lymphocyte function and T cell populations that normalized in parallel with
Idiopathic acute interstitial nephritis and uveitis associated with deafness

Fig. 3a,b. Audiograms before and after 3 weeks of systemic prednisone. (A) Basal audiogram showing a right hearing loss; (B) total recovery after therapy.

Serum Cr (mg/dl)

Fig. 4. Clinical course.

clinical improvement following steroid therapy [11]. Our patient showed hypergammaglobulinaemia (IgG), increased ESR, and the presence of mononuclear cells and granulomas in the interstitial infiltrate, suggesting an immunological disorder as a pathogenic factor.

Furthermore, our case presents another aspect of special interest: the development of sudden deafness that dramatically improved under systemic steroid treatment. Hearing loss in our patient was abrupt, severe, unilateral, and the direct cause was uncertain. Different immune disorders have been involved in the development of sudden deafness, such as a systemic type associated with vasculitis, including Cogan’s syndrome [12,13]. The immune pathogenesis is thought to involve immune complexes, cellular effectors, and/or circulating antibodies that may produce an inflammatory process involving inner ear structures [14–16]. The possibility of an immune aetiology for the sudden hearing loss in our patient is supported by the renal and ocular involvement and the clinical efficacy of steroid therapy [14].

To our knowledge, this is the first case reported of Dobrin’s syndrome associated with sudden hearing loss. The temporal relationship between renal and hearing involvement, laboratory data, kidney biopsy findings, and the excellent response of deafness and renal function to systemic steroids suggest an immunological disorder causing both the renal and ear involvement. Based on these findings, our patient could be diagnosed either as a variant of the original syndrome described by Dobrin et al. [3] or could represent a new manifestation of the same disorder.

References


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