Exceptional Case

Presence of autoantibodies against tubular and uveal cells in a patient with tubulointerstitial nephritis and uveitis (TINU) syndrome

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Introduction

Tubulointerstitial nephritis and uveitis (TINU) syndrome is characterized by acute tubulointerstitial nephritis with a favourable course and chronic recurrent uveitis. Since the first description in 1975 [1], more than 150 cases have been described in the literature [2]. Most of the patients with TINU syndrome are adolescents and young women, with a median age of onset of 15 (range 9 to 74) years. Renal tubulointerstitial infiltrates are primarily composed of activated lymphocytes, among which the helper/inducer T-cell subset is reported to be predominant [3,4]. In addition, TINU syndrome can be associated with granuloma in kidney or in another localization like bone marrow [1,5–7]. The pathogenesis of TINU syndrome remains unclear, but cell-mediated immunity, in particular delayed-type hypersensitivity, could play a large role in this disorder [8]. In addition, some studies suggest that uveitis and tubulointerstitial nephritis have a common immunological pathogenesis and so it was postulated that there may be a common antigenicity between renal and ocular tissues [3,9].

We report the first case of TINU syndrome associated with autoantibodies reacting to a possible common renal tubular and uveal antigen in a context of granulomatous inflammation.

Case

A 15-year-old boy with no past medical history presented with light sensibility, red eyes, ocular pain and small bilateral decrease in visual acuity with normal intraocular pressure. Slit-lamp examination showed cells and flare in the anterior chamber with small keratic precipitates but without corneal opacity. There were no nodules in the iris and in the anterior chamber angle. Anterior uveitis was diagnosed. On examination by ophthalmoscope, the retina and vitreous were normal. He then received atropine- and prednisone-based topical treatment. Asthenia and a 15-lb weight loss in 3 months were also noted. Family history was negative for vasculitis or renal disease. Blood pressure was normal.

On laboratory evaluation, serum creatinine was 1.27 mg/dL (112 µmol/L), peripheral white blood cell count was 10 × 10³/µL (10.49 × 10⁹/L) with 62% neutrophils and 27% lymphocytes. Urinalysis showed traces of proteins, 10–20 white blood cells/high-power field and no haematuria. In a random urine specimen, microalbuminuria was present. Complement was normal. Antinuclear antibodies, anti-double-stranded DNA, rheumatoid factor, anti-SS-A, anti-SS-B, cytoplasmic and perinuclear antineutrophil cytoplasmic antibody and lupus anticoagulant test results were negative. Serum angiotensin-converting enzyme concentration was normal. HLA-B27 was negative. Serum immunoglobulins were normal. Chest X-ray and abdominal ultrasound was unremarkable like cerebral RMN. A percutaneous renal biopsy was then performed.

The initial treatment consisted of prednisone at 1 mg/kg/day tapered over a period of 6 months. During the follow-up serum creatinine decreased over time of treatment and stabilized at 1.0 mg/dL (90 µmol); leucocyturia resolved after the treatment. Uveitis relapsed when prednisone dosage was 0.5 mg/kg/day; the patient was re-treated with topical prednisone; mycophenolate mofetil (500 mg po bid) was introduced and maintained at low-dose prednisone of 0.3 mg/kg/day. The patient was doing well with a remission of ocular symptoms at the last renal clinic.

Renal biopsy

Light microscopy analysis showed acute and chronic interstitial nephritis associated with a collection of epithelioid histiocytes and giant cells granuloma without caseous...
Fig. 1. (A) renal biopsy showed interstitial non-caseous granuloma associated with mononuclear infiltration (haematoxylin, eosin, saffron, ×100). (B) An immunohistochemistry study found that the majority of mononuclear cells were constituted of CD4+ cells (×100). (C) Indirect immunofluorescence with anti-IgG antibody with focal cytoplasmic staining in cortical tubular cells (×200). (D) Indirect immunofluorescence with anti-IgG antibody with membranous positivity in ciliary body cells, a part of uvea (×400). (E) Normal mouse eye with only DAPI counterstain: 1 Cornea, 2 Iris, 3 Lens, 4 Retina and 5 Ocular Muscle. The yellow square represent the area of analysis of F to H (×25). (F) DAPI counterstain in area of iris (×200). (G) Indirect immunofluorescence with anti-IgG antibody with focal membranous positivity in iris cells (×200). (H) Photograph is a merged image to reveal DAPI stain and indirect immunofluorescence with anti-IgG antibody (×200).
necrosis (Figure 1A). The nine glomeruli and the vessels were normal. Standard direct immunofluorescence was negative.

Immunohistochemical staining was performed using antibodies against CD3 (1/20, Rabbit, polyclonal, Labvision, CA), CD4 (1/20, mouse, monoclonal, Vector, CA) and CD8 (1/20, mouse, monoclonal, Vector, CA). Samples were then incubated with biotinylated immunoglobulins (LSAB II, DAKO, Glostrup, Denmark). This analysis showed that the majority of lymphocytes were CD4+ (Figure 1B).

**Indirect immunofluorescence**

Before treatment with oral corticosteroids, the patient's serum was withdrawn for further analysis. Informed consent was obtained from the patient and his parents. Indirect immunofluorescence studies were then performed. The serum of the patient and the serum of a normal healthy volunteer were placed for 1 h at room temperature on frozen sections of normal human kidney explanted for tumour nephrectomy and normal mouse eye. The slides were rinsed twice with PBS and standard antibodies against human IgG, IgA and IgM (1/20, rabbit polyclonal, FITC, Dako, Glostrup, DK) were then placed for 1 h at room temperature. The slides were counterstained for 10 sec with DAPI. The analysis in fluorescence microscopy showed focal cytoplasmic IgG deposits in tubular epithelial cells (Figure 1C) and membranous IgG deposits in uveal cells (Figure 1D, F, G, H), incubated with the patient's serum. Neither IgA nor IgM deposits were observed. In the kidney, the staining was diffuse in the cortical proximal and distal tubules but was not observed in the medulla. In the eyes, the expression was in ciliary body cells (Figure 1D) and in iris cells (Figures 1E–H). The expression was essentially present in the cell membrane. There were no deposits in sections incubated with normal serum.

In spite of the publication of more than 100 cases, the pathogenesis of TINU syndrome is still not well understood. It is postulated that TINU is an autoimmune disease involving both tubules and uvea and leading to the development of granuloma. Nevertheless, the nature of the antigens involved in this autoimmune process is not known. Furthermore, the presence of autoantibodies against both tubules and uvea has never been demonstrated. For the first time, we report a patient in whom antibodies against both tubular cells and uveal cells were found. Similar to our study, a previous report described autoantibodies against tubular cells in TINU syndrome [9]. Similar antibodies against tubular cells have also been found in the sera from patients with Sjögren's syndrome [10] or systemic lupus erythematosus [11]. Therefore, it has been suggested that the anti-tubular cells' antibodies may have developed secondary to tubular antigen exposure by injury. However, since our patient's serum contained anti-tubular and anti-uveal cells' antibodies, this hypothesis is very unlikely. Our findings suggest that antibodies against tubular cells and uveal cells have induced tubular and uveal injuries, thereby inducing nephritis and uveitis characterizing the TINU syndrome. Interestingly, despite the finding of antibodies against tubular cells by indirect immunofluorescence, the direct immunofluorescence study performed on a renal biopsy specimen of our patient failed to demonstrate IgG deposits. Nevertheless, direct immunofluorescence was negative in every study on TINU syndrome. This standard technique is probably less sensitive to detect autoantibodies than indirect immunofluorescence. Also in lupus, direct immunofluorescence with IgG usually fails to detect antibodies against nuclear cells, while patients' sera usually react with normal tissue such as kidney with an intense nuclear staining in indirect immunofluorescence.

Most of the studies describing immunohistochemical kidney analysis in TINU patients have demonstrated that interstitium is infiltrated mainly by T-cells together with monocytes/macrophages [12,13]. As shown in our patient, other reports have described that the helper/inducer T-cell subset was predominant in the renal interstitial infiltration in TINU [3,4], contrary to other cases, in which the majority of infiltrative cells were suppressor/cytotoxic T-cells [13]. This usual predominant CD4+ infiltration could participate in the formation of granuloma [1,5–7]. Our study proves that our patient has autoantibodies against, probably, common antigen situated in tubular and uveal cells. We hypothesize that this autoimmune disease involves a cellular-immune response mediated by CD4+ T-cells leading to granulomatous associated inflammation.

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**References**


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