NDT Plus (2009) 2: 300–302 doi: 10.1093/ndtplus/sfp048 Advance Access publication 28 April 2009

Case Report



Anti-CTLA-4 (CD 152) monoclonal antibody-induced autoimmune interstitial nephritis

Elaine C. Jolly¹, Menna R. Clatworthy², Christopher Lawrence¹, Paul D. Nathan³ and Ken Farrington¹

¹Renal Unit, Lister Hospital, Coreys Mill Lane, Stevenage, Hertfordshire SG1 4AB, ²Renal Unit, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ and ³Mount Vernon Cancer Centre, Rickmansworth Road, Northwood, Middlesex HA6 2RN, UK

Correspondence and offprint requests to: Elaine C. Jolly; E-mail: elainejolly@yahoo.co.uk

Abstract

Targeted immune-modulating agents are entering clinical practice in many specialties, providing novel therapeutic possibilities but introducing new potential toxicities. We present the first reported case, to our knowledge, of immune-mediated nephritis following the administration of Tremelimumab (CP-675, 206), an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody. High-dose steroid therapy led to a rapid improvement in renal function, avoiding the need for renal replacement therapy.

Keywords: acute renal impairment; CTLA-4 antibody; interstitial nephritis

Case report

A 41-year-old man with Stage IV malignant melanoma (MM) was referred to the renal services with acute renal impairment. His initial disease had been surgically managed several months previously, but a follow-up surveillance computed tomography (CT) scan demonstrated multiple metastases with intra-abdominal and retroperitoneal lymphadenopathy. He was, therefore, enrolled into a phase III clinical trial of an immune activating anticytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody.

At enrolment, his serum creatinine was 98 μ mol/L [eGFR 78 mL/min/1.73 m² (MDRD 4)], and he received a total dose of 1280 mg (15 mg/kg) anti-CTLA-4 antibody (Tremelimumab, CP-675, 206, Pfizer, Boehringer Ingelheim Pharma KG). One week later, he developed lethargy, nausea and vomiting. Blood tests revealed acute renal failure, with a serum creatinine 208 μ mol/L, which over the next week rose to 544 μ mol/L. Urinalysis showed a trace of blood but no red cell casts on microscopy. An ultrasound scan demonstrated unobstructed, normal-sized kidneys. An autoimmune screen revealed positive antinuclear antibody (ANA) to a titre of 1:320 (fine-speckled pattern), but nega-

tive double stranded DNA (dsDNA) and extractable nuclear antigen (ENA). Complement levels and immunoglobulins were normal. Anti-cardiolipin antibodies were negative, as were anti-neutrophil cytoplasmic antibody (ANCA), glomerular basement membrane antibody (GBM) and an autoimmune liver disease screen.

Examination showed that he was euvolaemic, hypertensive (165/90 mmHg) and had vitiligo. A subsequent renal biopsy (Figure 1) demonstrated an active inflammatory interstitial infiltrate. Stains for melanoma cells, S100, Melan-A and HMB45, were negative. Both electron microscopy and immunofluorescence excluded immunecomplex glomerulonephritis. Further stains identified the major infiltrating cell type as CD8⁺ T-lymphocytes. He was commenced on high-dose oral prednisolone (60 mg/day). Within 2 weeks, his creatinine had fallen to 195 µmol/L but then plateaued. A magnetic resonance urogram (MRU) confirmed the presence of large volume metastases in the retroperitoneum, abdomen and pelvis with consequent bilateral hydronephrosis and hydroureter. In the hope of preventing worsening ureteric obstruction in the face of disease progression, he was referred for bilateral ureteric stenting. The serum creatinine fell to 114 µmol/L, and prednisolone therapy was consequently weaned (Figure 2). He subsequently received dacarbazine chemotherapy but sadly died from irreversible disease progression a few months later.

Discussion

Biological agents that target specific elements of the immune response are increasingly used in the treatment of autoimmune diseases and cancers, including MM. MM is increasing in incidence in the UK [1], and patients with advanced disease have a poor response to conventional treatment. Immunotherapy in MM is aimed at breaking tolerance to tumour-specific self-antigen, thus facilitating clearance of cancer cells by the patient's own immune system. Treatments trialled include those stimulating generalized effector T cell activation, such as recombinant interferon alpha (IFN- α) and interleukin-2 (IL-2) [2], and those aimed at

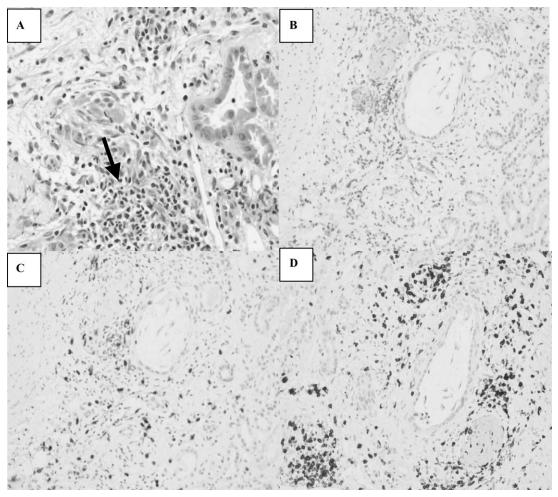


Fig. 1. (A) Native renal biopsy showing an active inflammatory infiltrate in the interstitium (arrow) (H+E). (B) Immunohistochemical preparation for pan-T cell marker CD3. (C) CD4 staining. (D) CD8 staining.

promoting a tumour-specific immune response, for example vaccination with a tumour antigen [3] or with tumour antigen-loaded dendritic cells [4].

CTLA-4 (CD 152) is a molecule expressed on T cells following activation and provides an internal mechanism by which T cells can limit or terminate an immune response. Blockade of CTLA-4 with an antagonist monoclonal antibody such as Tremelimumab (CP-675, 206) promotes T cell activation [5] and inhibits the maintenance of self-tolerance. However, this loss of self-tolerance is not tumour specific and can lead to the development of a variety of autoimmune diseases, termed immune-related adverse events (IRAEs). Other strategies promoting generalized effector T cell activation such as the administration of IFN- α and IL-2 are also associated with the development of autoimmunity [6,7].

Two humanized CTLA-4 monoclonal antibodies—Ipilimumab/MDX-010 (Medarex, Bristol-Myers Squibb) and Tremelimumab (CP-675, 206) (Pfizer)—are in clinical development for the treatment of a variety of malignancies including MM, renal cell, ovarian and colonic carcinoma. Phase III data are awaited for both drugs. Ipilimumab has been shown to induce a clinical response in a small minority of patients, but its use is associated with the development of

a number of autoimmune phenomena including dermatitis, enterocolitis, hypophysitis and one case of nephritis [8–10]. Enterocolitis is the most common IRAE observed affecting up to 20% of patients, and results in significant morbidity and mortality (four bowel perforations, one colectomy and two deaths [10]). High-dose steroid therapy settled symptoms in the majority of patients, without objectively reducing treatment response. Interestingly, objective tumour regression was associated with the occurrence of enterocolitis, emphasising the non-specific nature of the break in self-tolerance achieved through use of CTLA-4 antagonist antibodies.

The antibody our patient received (Tremelimumab, CP-675, 206), whilst demonstrating anti-tumour activity in a phase I clinical trial, also resulted in the development of autoimmune disease [11] (including enterocolitis, dermatitis, vitiligo, panhypopituitarism and autoimmune thyroid disease).

The patient we have described developed vitiligo, nephritis and detectable levels of ANA, presumably secondary to Tremelimumab (CP-675, 206) associated immune dysregulation. The temporal relationship between drug administration and presentation would support this theory, as would

302 E. C. Jolly *et al.*

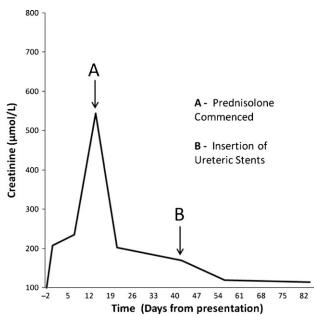


Fig. 2. Serum creatinine and response to treatment with A—corticosteroids and B—ureteric stents.

the T lymphocytic inflammatory infiltrate on renal biopsy, and prompt response to steroid therapy. The nephritis observed by Beck *et al.* [10] (personal communication) in one of their patients treated with Ipilimumab followed an almost identical clinical course to the one we observed (acute renal insufficiency, bland urinary sediment, interstitial nephritis on renal biopsy and prompt response to high-dose steroids). Furthermore, other groups have reported similar histological findings in skin [9,11], bowel [9,10] and liver [12] biopsies from patients displaying presumed autoimmune toxicity following anti CTLA-4 therapy.

It is difficult to determine whether the lymphocytic interstitial infiltrate observed in our patient was secondary to an immune reaction to drug antigens or a drug-induced loss of tolerance to self-antigens. The latter theory would fit with the additional clinical findings of positive ANA and vitiligo. Regardless of the mechanism of immune dysregulation, however, early intervention with high-dose steroids has proven efficacious in patients experiencing other organthreatening significant IRAEs [12].

Although the routine use of steroids in drug-induced interstitial nephritis is controversial, there is a growing body of evidence to suggest that early intervention with steroids after the culprit drug(s) has been discontinued helps to minimize the risk of interstitial fibrosis and permanent renal insufficiency [13]. If, as is more likely, the nephritis was autoimmune in nature, the benefit of steroid therapy is clearcut with the wealth of literature surrounding the treatment of systemic lupus erythematosus (SLE), particularly lupus nephritis [14], supporting such a therapeutic approach.

One final learning point from this case was the detection of an additional pathology. After an initial encouraging response to steroids, our patient's renal function plateaued at a higher baseline, despite prompt steroid

treatment. At this stage, an alternative pathology was sought and, indeed, obstructive uropathy secondary to tumour burden was identified. An improvement in serum creatinine to original baseline was achieved with bilateral ureteric stenting, facilitating further chemotherapy administration in the form of dacarbazine.

Acknowledgement. We thank Dr Meryl Griffiths, Consultant Histopathologist, Addenbrooke's Hospital for her pathological analysis of renal biopsy specimen, production of photographic material and accompanying comment.

Conflict of interest statement. None declared.

References

- Statistical Information Team, Cancer Research UK. Available at: http://info.cancerresearchuk.org/cancerstats/
- Hauschild A, Weichenthal M, Balda BR et al. Prospective randomized trial of interferon alfa-2b and interleukin-2 as adjuvant treatment for resected intermediate- and high-risk primary melanoma without clinically detectable node metastasis. J Clin Oncol 2003; 21: 2883–2888
- van Baren N, Bonnet MC, Dreno B et al. Tumoral and immunologic response after vaccination of melanoma patients with an ALVAC virus encoding MAGE antigens recognised by T cells. J Clin Oncol 2005; 23: 9008–9021
- Escudier B, Dorval T, Chaput N et al. Vaccination of metastatic melanoma patients with autologous dendritic cell (DC) derivedexosomes: results of the first phase I clinical trial. J Transl Med 2005; 3: 10
- Maker AV, Attia P, Rosenberg SA. Analysis of the cellular mechanism of antitumor responses and autoimmunity in patients treated with CTLA-4 blockade. *J Immunol* 2005; 175: 7746–7754
- Gogas H, Ioannovich J, Dafni U et al. Prognostic significance of autoimmunity during treatment of melanoma with interferon. N Engl J Med 2006; 354: 709–718
- Moschos SJ, Mandic M, Kirkwood JM et al. Focus on FOCIS: interleukin 2 treatment associated autoimmunity. Clin Immunol 2008; 127: 123–129
- Phan GQ, Yang JC, Sherry RM et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci USA 2003; 100: 8372–8377
- Sanderson K, Scotland R, Lee P et al. Autoimmunity in a phase I trial
 of a fully human anti-cytotoxic T-lymphocyte antigen-4 monoclonal
 antibody with multiple melanoma peptides and Montanide ISA 51 for
 patients with resected stages III and IV melanoma. J Clin Oncol 2005;
 23: 741–750
- Beck KE, Blansfield JA, Tran KQ et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. J Clin Oncol 2006; 24: 2283–2289
- Ribas A, Camacho LH, Lopez-Berestein G et al. Antitumor activity in Melanoma and anti-self responses in a phase I trial with the anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody CP-675,206. J Clin Oncol 2005; 23: 8968–8977
- Weber J. Review: anti-CTLA-4 antibody Ipilimumab: case studies of clinical response and immune-related adverse events. *Oncologist* 2007; 12: 864–872
- Gonzalez E, Gutierrez E, Galeano C et al. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int 2008; 73: 940–946
- Kimberly RP, Lockshin MD, Sherman RL et al. High-dose intravenous methylprednisolone pulse therapy in systemic lupus erythematosus. Am J Med 1981; 70: 817–824