Case Report

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Atezolizumab Associated Rapidly Progressive Pauci-Immune Glomerulonephritis: A Case Report

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ANNOTATION

Immune Checkpoint Inhibitors (ICI) are increasingly prescribed as therapy for a broad spectrum of cancers and have over the past decade contributed to revolutionizing the oncology field. While these humanized monoclonal antibodies have significantly improved survival rates, they are also associated with a variety of autoimmune adverse events. The number of therapies available on the market is growing, while the literature and knowledge of immune-related toxicities and nephrotoxicity of ICI are still limited. Herein, we present a patient with a metastatic small cell lung cancer treated with atezolizumab, an IgG1 monoclonal antibody aimed at the programmed death ligand 1 (PD-L1) of the tumor cell, who presented after 8 months of therapy with rapidly deteriorating kidney function, new onset of glomerular hematuria and proteinuria. Immunological analysis revealed positive PR3-ANCA and renal biopsy showed acute necrotizing pauci- immune glomerulonephritis with necrosis and crescents. High-dose intravenous methylprednisolone were prescribed followed by oral prednisolone with slow tapering and progressive improving of renal function. Atezolizumab was permanently discontinued.

Keywords: Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis; Atezolizumab; Immune-Related Adverse Effects; Pauci-Immune Glomerulonephritis; Immune Checkpoint Inhibitors; Kidney Injury

Abbreviations: AIN: Acute Interstitial Nephritis; AKI: Acute Kidney Injury; AIN: Acute Tubular Interstitial Nephritis; AE: Adverse Effects; irAEs: Immune-Related Adverse Effects; ASCO: American Society of Clinical Oncology; ANCA: Antineutrophil Cytoplasmic Antibodies; ANA: Antinuclear Antibody; PR3 Anti-Proteinase-3; MPO: Myeloperoxidase; ICI Immune Checkpoint Inhibitors; NSAID: Non-Steroidal Anti-Inflammatory Drug; PPI: Proton Pump Inhibitor

Introduction

Immune Checkpoint Inhibitors (ICI) have revolutionized the treatment of a broad spectrum of cancers, including hematologic malignancies, melanoma, non-small lung cancer, urothelial and renal cell carcinoma [1,2]. They are also widely used as an adjunct to surgery, chemotherapy and radiotherapy [3]. The widespread use of ICI has considerably improved overall outcome and survival of patients with advanced cancer. These monoclonal antibodies target inhibitory receptors and ligands expressed on immune cells (lymphocytes, T cells, antigen presenting cells) and tumor cells blocking pathways called immune checkpoints [4]. ICI inhibit three main down-regulating immune pathways: cytotoxic T-lymphocyte-antigen 4 (CTL4, ipilimumab/tremelimumab), programmed cell death protein 1 (PD-1, nivolumab, pembrolizumab cemiplimab) or its ligand (PD-L1, atezolizumab, avelumab, durvalumab) with the aim of generating an anti-tumor activity [1,4]. The activated T-cell infiltrates normal tissue and reacts not selectively, which leads to an uncontrolled stimulation of the immune system causing diverse immune-related Adverse Effects (irAEs), including general Adverse Events (AEs) and organ specific AEs of diverse magnitude that can appear in different stages of treatment [1,5]. The most frequently involved systems are gastrointestinal tract, the skin, the endocrine system and the liver. Current literature indicates a broad incidence rate from 15 to 90% [1]. Acute kidney in-

juries associated with atezolizumab are described [3], but literature about more accurate description of atezolizumab-associated renal AEs is still lacking and under-reporting or misdiagnosis may underestimate the real incidence [6].

Case Report

A 83-year-old patient was presented at the emergency department due to a deterioration of general condition and mild dyspnea. 8 months earlier, he was diagnosed with small cell lung cancer with diffuse osseous metastasis and had initially 4 cycles of combined chemotherapy with carboplatin, etoposide and atezolizumab for 3 months. This was followed by a maintenance therapy with atezolizumab (1200 mg every 3 weeks) for 4 months. His past medical history was significant for COPD Gold 1 and his kidney function was normal. Prior to admission, his medication was Dutasterid/Tamsulosin, an antivertiginosum (Cinnarizin/ Dimenhydrinat), calcium/vitamin D3 and an inhalation therapy with Vilanterol/Umeclidinium. On physical examination, vital signs included blood pressure of 162/74 mmHg, heart rate of 96/min. Lung auscultation revealed only a slight wheezing. Laboratory examination showed an Acute Kidney Injury (AKI) grade 3 [7] with a creatinine of 432 umol/l, eGFR of <15 ml/min and urea of 23.8 mmol/l. A moderate inflammatory syndrome was also present (total leukocyte count of 11.5 per microliter (norm: 10.0 G/l) and CRP of 79 mg/l (norm: <5 mg/l). The urine analysis revealed a non-nephrotic range proteinuria and a glomerular hematuria; phase-contrast microscopy showed dysmorphic erythrocytes and erythrocytes cylinders. Renal ultrasonography showed normal-sized kidneys, excluded obstruction and any renal perfusion disorders.

Supplemental laboratory tests were performed for further clarification. Hepatitis B, C and HIV serology were negative. The serum protein electrophoresis showed non- specific dysproteinemia, while the immunofixation revealed no monoclonal immunoglobulin. The free light chains were slightly elevated, but kappa/lambda ratio remained normal. The C3, C4 and antinuclear antibody (ANA) were within normal limits. Serological testing for anti-proteinase-3 (PR3) antibodies (ANCA) was positive with a titer of 199.9 IU/ml (norm: < 5 IU/ml). A thoracic CT-scan showed the known lung emphysema and no new pathologies. The renal biopsy showed three of six glomeruli being globally sclerotic, one tuft necrosis with fibrin extravasates and two cellular crescents. Furthermore, it showed signs of tubulointerstitial nephritis. The immunofluorescence showed no immune-complex deposits; immunoglobulin and complement were all negative. In view of the above, the diagnosis was consistent with acute necrotizing pauci-immune PR3-ANCA vasculitis associated with atezolizumab therapy. Atezolizumab was permanently discontinued and immunosuppressive therapy with intravenous pulses of methylprednisolone (500 mg daily for 3 days), followed by daily oral methylprednisolone (1mg/kg/d) with gradual tapering was started.

After 12 weeks the creatinine halved from its peak of 460 umol/l to 233 umol/l and the tapered daily corticosteroid dose of 7.5 mg was continued. Over 6 months the renal function gradually improved (serum creatinine 181 umol/l, eGFR 30 ml/min/1.72m2) with a decreased albuminuria of 400 mg per day and disappearance of hematuria. Also, the PR3-ANCA Titer decreased to 12.1 IU/ml. Additional immunosuppressive therapy was not necessary (Figure 1).

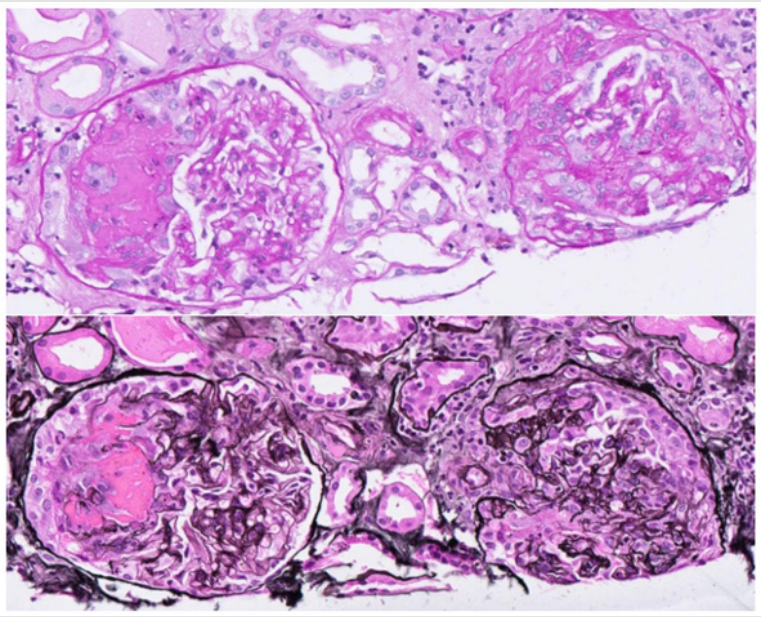

Figure 1: Two glomeruli in Periodic acid–Schiff stain (above) and Methenamine silver-HE: One glomerula with an early cellular crescent associated with necrosis of the tuft and rupture of the capillary wall (left) and one glomerula with a cellular crescent and collapsed capillary loops showing disruption of the glomerular basement membrane (right).

Discussion

Kidney injuries can occur during a treatment with ICI, but the incidence is likely underestimated [4]. They have an incidence rate of 3-5 % less frequently reported as other irAEs and belong to the most delayed ones [1,8,9]. Compared to monotherapy, the incidence rate increases with combined immunotherapy by 1-2% to 5% [4,9]. The CTLA-1 and PD1 inhibitor therapy combination appear to be the most risk-prone [10]. Furthermore, atezolizumab had the strongest association with renal AEs among all ICI monotherapy regimens [6]. On the other hand, Tie et al's systematic review presents a different perspective, stating that atezolizumab results in fewer irAEs because it permits the co-activation of PD-1 and PD-L2, making it a more manageable and safer option [5]. Concomitant therapy of ICI with other medications like proton pump inhibitor (PPI), non-steroidal anti- inflammatory drug (NSAID) or antibiotic carries an increased risk of kidney injury [10]. Furthermore, older age, lower baseline kidney function, hypertension, prior- or concomitant irAEs, pre-existing genitourinary malignancy and others nephrotoxic medication (antibiotics, NSAID, cisplatin and carboplatin) were independently associated with AKI [3,8]. The reported patient had initially a chemotherapy with carboplatin, which could represent a significant co-factor in this case. A 2019 systematic review revealed that the primary adverse events associated with atezolizumab were predominantly observed in the gastrointestinal, dermatological, and respiratory systems, as well as encompassing general disorders.

The documented occurrence of AEs with a severity grade exceeding 3 was minimal, with respiratory symptoms and pneumonitis observed in 1.3% of cases [5]. Cortazar et al observed a frequent rate of extra-renal irAEs occurring concomitantly or immediately preceding the AKI [11]. Our patient suffered a deterioration from both general condition and respiratory status. As described above, dyspnea is one of the most common respiratory symptoms related to atezolizumab [5]. The thoracic CT-scan did not show any new lung abnormalities and following the discontinuation of atezolizumab therapy, the dyspnea also improved. ICI are mainly cleared by proteolytic degradation in the liver [12]. As the kidney does not excrete it, there is no need for dose adjustment for patients with kidney failure [13]. The half-life of the ICI depends on the specific ICI agent. For example, atezolizumab lasts for 27 days and avelumab up to 6 days [12]. The reported time from ICI initiation and onset of AKI ranged from 6 up to 37 weeks, with a median time of 14 weeks. In therapies with anti-PD-1 and/or anti-PD-L1 antibodies, an AKI was reported from 3 to 12 months after the start [9]. Our patient was within this time range as he had 6 months after the start of the treatment with atezolizumab an AKI grade 3.

Several types of kidney injuries have been described in association with ICI therapy. Acute tubular interstitial nephritis (AIN) is the most common pattern of injury detected in > 90% of patients who underwent a renal biopsy. The underlying pathological mechanism is believed to involve a breakdown in self-tolerance towards self-renal antigens [9]. The simultaneous use of treatments known to induce an AIN, such as NSAIDs, PPIs or antibiotics, has been identified as a risk factor. This leads some authors to postulate that ICIs trigger an autoimmune response in T-cells against these nephrotoxic agents [9]. In contrast to AIN, glomerular diseases associated with ICI have received less extensive documentation, and in 41% of instances, like in our patient's case, they are concomitant with tubule-interstitial injury [14]. Acute pauci-immune glomerulonephritis, minimal change disease and C3 glomerulopathy are the most frequent glomerular diseases with a reported frequency of 27%, 20% and 11%, respectively [1,14]. The pathology between ICI use and glomerular diseases remains unclear [14]. A T-cell over-activity leading to an inflammatory reaction could be a possible pathophysiological mechanism. Furthermore, it is assumed that CTL4-4 receptors on the CD8+ T-cells may activate polymorphonuclear-cells. The exposure of the PR- 3 and MPO antigen on the surface of the polymorphonuclear-cell may react with ANCA. Kitchlu et al. [14] reported that of the 12 published cases of pauci-immune glomerulonephritis, ANCA serologies were positive by only 2 patients, leading to the assumption that most cases are ANCA negative vasculitis. He postulated that these are a certain epitope to which ANCA is reacting, but those epitopes are not detected with currently available assays [14].

Aqeel et al. suggested that ICIs, specifically PD-1 inhibitors, could cause de novo or even trigger a relapse of an ANCA associated vasculitis [15]. Further kidney lesions like acute tubular injury, anti-glomerular basement membrane disease and C3 glomerulonephritis are described less frequently. Cases of thrombotic microangiopathy have shown to be often limited to renal parenchyma without systemic hemolytic anemia and schistocytosis. Finally, ICIs have also been associated with an increased risk of rejection in kidney transplant patients, especially those receiving an anti-PD1 treatment [9]. Only a minority of patients are referred to a nephrologist. This means that the diagnosis is often missed or delayed. Close monitoring of kidney function is essential before the start of treatment and throughout its duration. In this regard, the American Society of Clinical Oncology (ASCO) guidelines help to establish management strategies. In the case of any non-functional AKI with signs of glomerular involvement, referral to a nephrologist with reassessment of the indication for a kidney biopsy is strongly recommended [2].In terms of management strategy, it is advisable to withhold ICI and to introduce corticosteroid treatment (0.5-1 mg/kg/day sometimes preceded by intravenous pulse-dose corticosteroids for 3 days) when AKI is severe (AKI > 2). No tapering therapy has been prospectively evaluated, and treatment may need to be continued for longer periods (> 4 weeks to 3 months).

If no renal improvement additional immunosuppression (infliximab, azathioprine, cyclophosphamide [monthly], cyclosporine, and mycophenolate) should be considered [2]. Response to treatment is variable, with a better response rate in the case of AIN (> 85% re-

sponse rate); glomerular disease has a poorer long-term prognosis [11]. The reported patient was treated with corticosteroids and showed a partial kidney recovery. To suppress the persistent inflammation the steroid therapy was continued with a very low dose and no steroid-induced complications were found. There is a lack of consensus on whether immune therapy should be started again after a renal injury. The reported recurrence rate also differs between studies, which can be explained by immunotherapy at the evaluation criteria to reuse ICI can differ [10]. If ICI remains the only therapeutic option for an effective treatment, a challenge should be considered. Individualized treatment and good collaboration between nephrologists and oncologists are crucial to evaluate patient- and cancer-related factors while taking into account the risk- benefit ratio. Our patient did not receive again atezolizumab as the renal recovery took a long time and as there was still an option of rechallenging with Carboplatin and Etoposid.

Conclusion

In conclusion, ICIs have revolutionized the management of advanced cancers despite sometimes severe AEs. Early referral and individualized treatment is essential. Cessation of ICI is strongly encouraged and treatment with corticosteroid is recommended. Here, we have reported a case of biopsy-proven acute necrotizing pauci-immune vasculitis, following therapy with atezolizumab for lung cancer, which evolved relatively favorably after treatment.

Conflict of Interest

The authors declare no conflict of interest.

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