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LESSONS FOR THE CLINICAL NEPHROLOGIST

Everolimus-associated alveolar hemorrage relapse after drug discontinuation in a kidney transplant recipient

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The Case

We report the case of a 51-year-old man affected by End Stage Renal Disease due to diabetic nephropathy, who received a kidney transplantation from a deceased donor. After induction with basiliximab and high dose intravenous methylprednisolone boluses, the patient was on maintenance immunosuppression with methylprednisolone, tacrolimus and everolimus. Everolimus was chosen in order to minimize calcineurin inhibitor levels in a patient with a long history of post-surgical diabetes mellitus. Major comorbidities and other medications are reported in the Supplementary Materials.

Two months after transplantation, the patient started suffering from dyspnoea and haemoptysis, in the absence of other associated symptoms. He was conscious, hemodynamically stable and apyretic, and rhinopharyingeal swab for Sars-CoV-2 was negative. During this period, everolimus and tacrolimus trough levels always remained within the optimal ranges (3–8 ng/ml and 2–4 ng/ml, respectively). Chest auscultation revealed diffuse inspiratory crackles and expiratory wheezing in both lungs. Chest X-ray showed bilateral alveolar micronodules with interstitial thickening. Subsequently the patient underwent high resolution CT scan (HRCT) that showed bilateral multiple "ground-glass" areas and infiltrates consistent with alveolar haemorrhage (Fig. 1: day 1 (a), day 17 (b), day 20 (c) and at 2-month follow up (d)).

Empiric antibiotic therapy with piperacillin/tazobactam was started though with no response. Five days later, blood tests showed severe anaemia (Hb 7.2 g/dL), renal function impairment (eGFR 21 ml/min vs 35 ml/min), with normal white blood cell and platelet counts and C-reactive protein levels.

Everolimus was discontinued and the patient was admitted to the Nephrology Unit: arterial blood gas analysis showed severe respiratory insufficiency requiring high-flux oxygen therapy. A red blood cell transfusion was performed. Further blood tests documented negative ANA, ANCA and AntiGBM antibodies. Blood and sputum cultures were negative, as were Quantiferon TB and polymerase chain reaction for CMV, EBV and BKV DNA.

Fibrobroncoscopy was performed and broncho-alveolar lavage (BAL) showed progressively more bloody samples, typical of diffuse alveolar haemorrhage, which tested negative for bacterial, viral and fungal cultures; cytological evaluation detected several hemosiderin-laden macrophages (>20%) (Fig. 2).

During hospitalization his clinical picture progressively improved with normalization of gas exchanges. Follow-up HRCT revealed global regression of the pathologic findings, albeit without complete resolution. Considering the rapid response to everolimus discontinuation, once other infectious and immunological differential diagnoses were excluded, a diagnosis of everolimus-related non-infectious pneumonitis was made.

Therapy with high-dose intravenous steroids was considered, but not prescribed due to the rapid improvement of the clinical picture. The patient was discharged under immunosuppression with methylprednisolone and tacrolimus.

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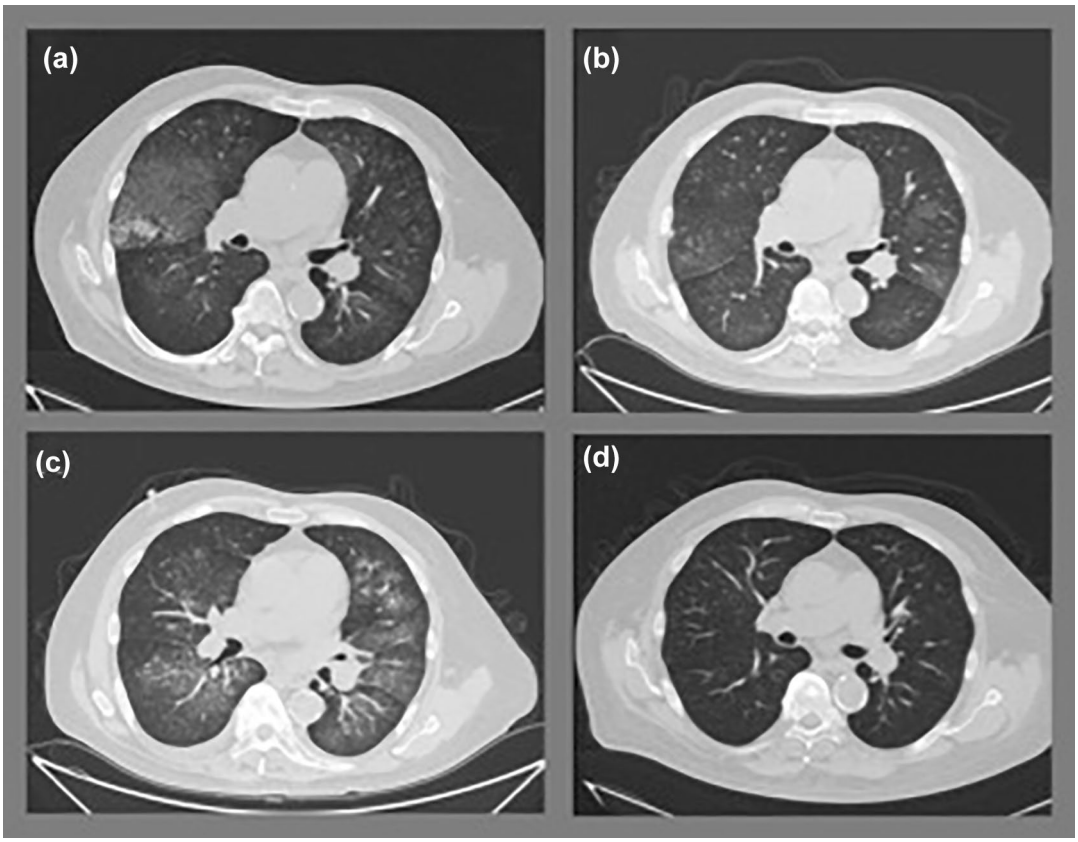

Fig. 1 HRCT scan on day 1 (**a**), day 17 (**b**), day 20 (**c**) and at a 2-month follow up (**d**).

However, the patient was re-admitted ten days later due to a relapse of dyspnoea, haemoptysis and asthenia. New blood tests showed a relapse of severe anaemia and HRCT revealed worsening of the "ground-glass"-like areas and alveolar haemorrhage.

Pulses of intravenous steroids the clinical picture progressively improved up to complete resolution of symptoms, that led to hospital discharge.

Rapid tapering of steroids to the maintenance dose (prednisone 5 mg daily) was carried out and currently, after 12 months of follow-up, no relapse has occurred.

Clinical course is summarised in Fig. 3.

Lesson for the clinical nephrologist

Adverse events observed in patients undergoing systemic treatment with mammalian target of rapamycin (mTOR) inhibitors include pulmonary dysfunction (non-infectious pneumonitis), epithelial-cutaneous events (stomatitis, rash), metabolic dysfunction (elevated blood levels of glucose and lipids), and immune suppression (infections).

MTOR inhibitors are commonly used for cancer treatment and as immunosuppressants to prevent rejection of solid organ transplants. Everolimus, sirolimus and temsirolimus belong to this class of drugs and are generally well tolerated (1).

The most common side effects related to everolimus include stomatitis, cutaneous rash, metabolic dysfunction, infections, oedema, proteinuria and difficult wound healing (2), while pulmonary toxicity is a rare complication that occurs in up to 16% of patients receiving this mTORi as chemotherapy and in 4.3% of transplant recipients receiving everolimus as an immunosuppressant (1, 3).

The cause of this potentially serious adverse event is not yet fully understood. Rapamycin and its derivatives can induce autophagy in cells by inhibiting mTORC1, thus causing phosphorylation of pro-autophagic kinases and determining autophagosome formation and possible exposure of antigens on alveolar endothelial cells,which may explain a lymphocyte-mediated toxicity (4). On the other hand, the clinical response to corticosteroids and discontinuation of everolimus, together with T-cell lymphocytosis often reported in bronchoalveolar lavage, suggests a hypersensitivity mechanism (1). According to another hypothesis, the high affinity of sirolimus for plasma proteins may render it immunogenic as a hapten, thus triggering a T-cell reaction against the antigen complex (5). Direct toxicity may

Fig. 2 Bloody samples from broncho-alveolar lavage fluid

be suggested by the greater rates of pneumonitis occurring in patients receiving high doses of mTORi and by the fact that discontinuation of therapy is necessary to allow early remission of the symptoms (6, 7). Furthermore, pulmonary toxicity does not seem to be related to longer drug exposure and/or higher blood levels, since many reports of pneumonia are described in patients whose everolimus levels are within therapeutic range (4, 6).

Once the diagnosis is made, clinical management largely depends on the severity of the symptoms. Light to moderate cases usually benefit from drug dose reduction or discontinuation and oral corticosteroid therapy (7), while the literature regarding a therapeutic shift from everolimus to another mTORi is controversial (7, 8). Patients with severe to potentially deadly clinical pictures showed good response to everolimus discontinuation and high-dose intravenous corticosteroid therapy, which should be administered while the evaluation is on-going if there is a solid clinical suspicion of non-infectious pneumonitis (1, 7).

We report the case of a transplant recipient who developed severe respiratory insufficiency due to alveolar haemorrhage, confirmed by fibrobronchoscopy, under everolimus treatment. Bacteriological, mycobacteriological and viral tests allowed excluding the most common infectious aetiologies; auto-immune study was also negative. The clinical picture was not modified by broad spectrum antibiotic therapy, and indeed, it was responsive to everolimus discontinuation. After observing an initial rapid clinical resolution of symptoms and radiological signs of improvement, a relapse of the clinical picture occurred almost 20 days after the discontinuation of everolimus, which resolved only after intravenous pulse steroids. Relapse of symptoms after everolimus discontinuation might lead us to speculate that

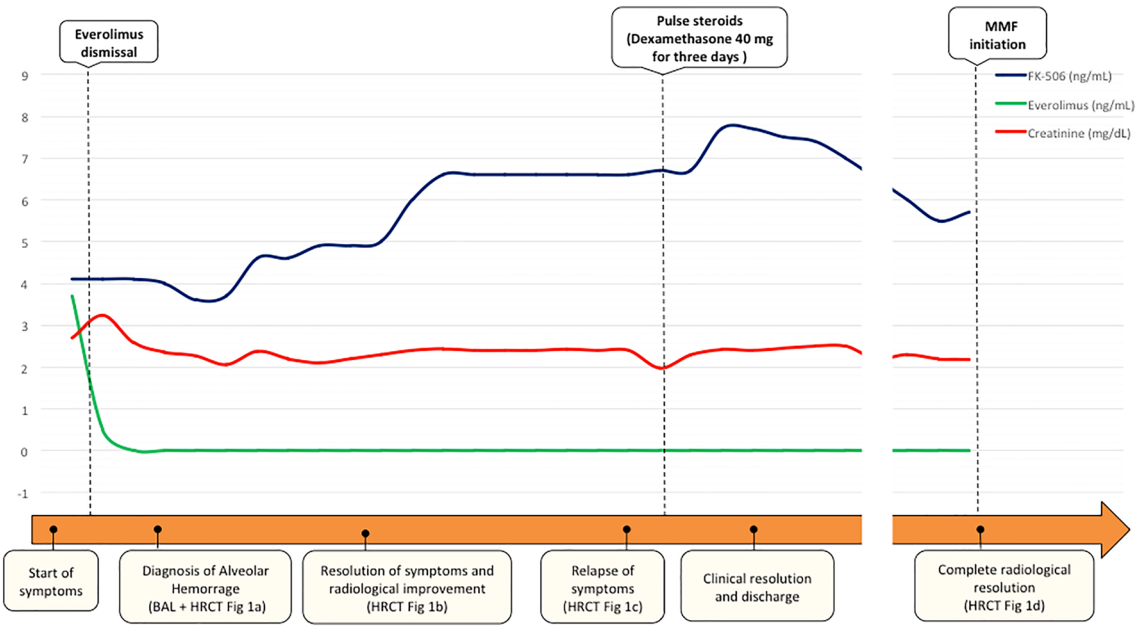

Fig. 3 Timeline of clinical course and drug administration

the first diagnosis was wrong, however, after this episode no other relapses were observed during 12 months of follow-up with standard low-dose steroid maintenance therapy.

Non-infectious pneumonia related to everolimus is a rare and potentially harmful complication that must always be considered in the differential diagnosis in patients receiving mTOR inhibitors and complaining of non-specific respiratory symptoms, with or without systemic conditions like fever or asthenia. Accurate management of this class-related side effect is crucial, and the clinical approach must be tailored to the severity of the condition. Pulmonary function tests were not performed in the reported case. Of note, the use of diffusing capacity of the lung for carbon monoxide (DLCO) combined with HRCT scan has been proposed in an algorithm for surveillance of fragile patients (such as recipients of solid organ transplants), especially when more than one drug with known pulmonary potential toxicity is simultaneously administered (9).

This is not the first reported case of everolimus-related pneumonitis in the literature, however, it may suggest paying attention to some peculiar aspects: the severity of presentation with alveolar haemorrhage and a late relapse after drug discontinuation. Improvement of symptoms should not be overestimated since relapse is possible, and the most severe cases, lithe the one here described, may require high dose intravenous steroid administration to achieve complete remission.

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Declarations

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Ethical Approval This article does not contain any studies with human participants or animal performed by any of the authors.

Informed consent Informed consent has been obtained from the patient.

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