

IS EVEROLIMUS INVOLVED IN THE PATHOGENESIS OF IMMUNOTHROMBOCYTOPENIA IN A RENAL TRANSPLANT RECIPIENT WITH RENAL ADENOCARCINOMA?

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DEAR EDITOR,

Thrombocytopenia is frequent in renal transplant recipients and is most commonly caused by suppression of the bone marrow, especially in the early stage of transplantation (1). Paraneoplastic syndromes are a group of malignancy-associated disorders that occur due to immune response to the tumor or hormones produced by tumor itself. Some cases can present as immune-mediated hematological diseases, such as immune thrombocytopenia (ITP) (2). These can present prior to the cancer diagnosis, concurrent with cancer or in a period of complete remission. Recent meta analysis showed that autoantibody testing in ITP patients has a high specificity but low sensitivity, and concluded that a positive autoantibody test can be useful for ruling in ITP, but a negative test does not rule out ITP (3). Paraneoplastic ITP associated with renal cancer after renal transplantation has not been reported. A 43-year-old male patient with end-stage renal failure due to sepsis after the war-injury had replaced his renal function with hemodialysis from 1996 until 2003 when he received a renal allograft from a deceased donor. Immunosuppressive regimen included cyclosporine, mycophenolatemofetil and steroid, with no other concomitant drugs. The posttransplant course was uneventful until 2019 when his right native kidney was removed due to finding of a complicated Bosniak type IV cyst in his native kidney on routine examination. Eventually, patohistology verified the mass

to be a clear cell renal carcinoma, staged pT3aN0R0. Postoperatively, cyclosporine was replaced with everolimus. Three months later, patient had developed petechial rash on lower extremities. Laboratory examination verified severe thrombocytopenia [$10 \times 10^9/L$] with stable allograft function and normal findings of other laboratory parameters. Hematologic workup revealed positive IgG anti-human platelet antibodies on glycoprotein Ia/IIa complex (GP Ia/IIa) in serum, thus implying of possible immune etiology of thrombocytopenia. Patient responded well to 3 days of therapy with 6-methylprednisone pulses (125 mg each) and platelet count increased to $60 \times 10^9/L$. However, in the further follow-ups, patient's platelet count decreased to $34 \times 10^9/L$, thus therapy with eltrombopag has been introduced (1x50 mg per day) what resulted with increase of platelet count to $110 \times 10^9/L$ and their stabilization at this level. Rituximab was not used in order to avoid further immunosuppression in the context of malignancy but also due to the beginning of the COVID-19 pandemic. After 12 months of follow-up our patient has no residual or recurrent cancer as determined by computerized tomography.

Paraneoplastic ITP most commonly occurs in patients with lung and breast cancer and, although rare, there had been some published cases of this phenomenon in renal cell cancer. In most patients, it responded well to steroids (4).

The only change in medications in our patient was replacement of cyclosporine with everolimus. Everolimus is approved for use in kidney and liver transplant patients, and is used for prophylaxis for organ rejection. Some patients who had undergone this therapy showed increased rate of thrombocytopenia (5). In the context of positive antithrombocyte antibodies, the most probable cause of thrombocytopenia is paraneoplastic syndrome. However, everolimus, although reported to improve paraneoplastic immunothrombocytopenia (6) may contribute to development of immunothrombocytopenia by decreased suppression of antibody production in general. Namely, everolimus was suspected initially to be associated with an increased risk of donor specific antibody production (7), what neither was not case in our patient, nor was found in large studies including the TRANSFORM study (8). GPIIb/IIIa antibodies were reported in a patient with renal cancer (9), and were negative in our patient. Possible explanation for positive GP Ia/IIa but not GPIIb/IIIa might be performance characteristics of autoantibody testing especially with low number of platelets as was present in our patient (3).

In conclusion, patients with thrombocytopenia after renal transplantation should undergo careful diagnostic evaluation and paraneoplastic origin of symptoms should be considered in the differential diagnosis. Everolimus may be involved in development of immunothrombocytopenia by allowing antibodies production.

We declare that this manuscript is original and has not been published before or currently being considered for publication elsewhere.

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We submit this case report with consent given by a case patient.

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