Late Acute Cellular Rejection After Anakinra Treatment in a Kidney Transplant Patient, Is It a Coincidence?

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Familial mediterranean fever (FMF) is an autosomal recessive auto-inflammatory disorder, which could lead to secondary (AA) amyloidosis. Anakinra is an IL-1 receptor blocker and a treatment option for patients with FMF. There is no reported rejection episode associated with the use of Anakinra in the literature. A forty-nine years old woman with a history of kidney transplantation is described here. Anakinra was initiated in the patients whose FMF attacks were exacerbated, and the inflammation could not be controlled under the colchicine treatment. After eight months of follow up under Anakinra treatment, a moderate but persistent increase in serum creatinine level was observed. Allograft biopsy was compatible with acute T cell-mediated rejection with BANFF type 2A. Data on the use of Anakinra in KTRs is limited. Anti-drug-antibodies or hapten induced T cell activation may facilitate late-onset acute T cell-mediated rejection in the patient who used Anakinra.

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Case Report

INTRODUCTION

Familial mediterranean fever (FMF) is an autosomal recessive auto-inflammatory disorder which is characterized by lifelong recurrent self-limiting attacks of fever and systemic inflammation.[1] Progressive secondary (AA) amyloidosis is the primary cause of mortality and morbidity in patients with FMF. Renal amyloidosis leads to proteinuria, and end-stage kidney disease develops 2 to 13 years after the onset of proteinuria.[2] Anakinra (Kineret;r-metHuIL-1ra) is a recombinant human interleukin-1(IL-1) receptor antagonist that inhibits the activity of both IL-1α and IL-1β and seems to be safe and effective alternative treatment option for patients with FMF who do not respond to colchicine.[1,3]

Here, we report acute T cell-mediated rejection (ACR) episode that occurs after Anakinra use in a 49-year-old woman with kidney transplantation.

CASE REPORT

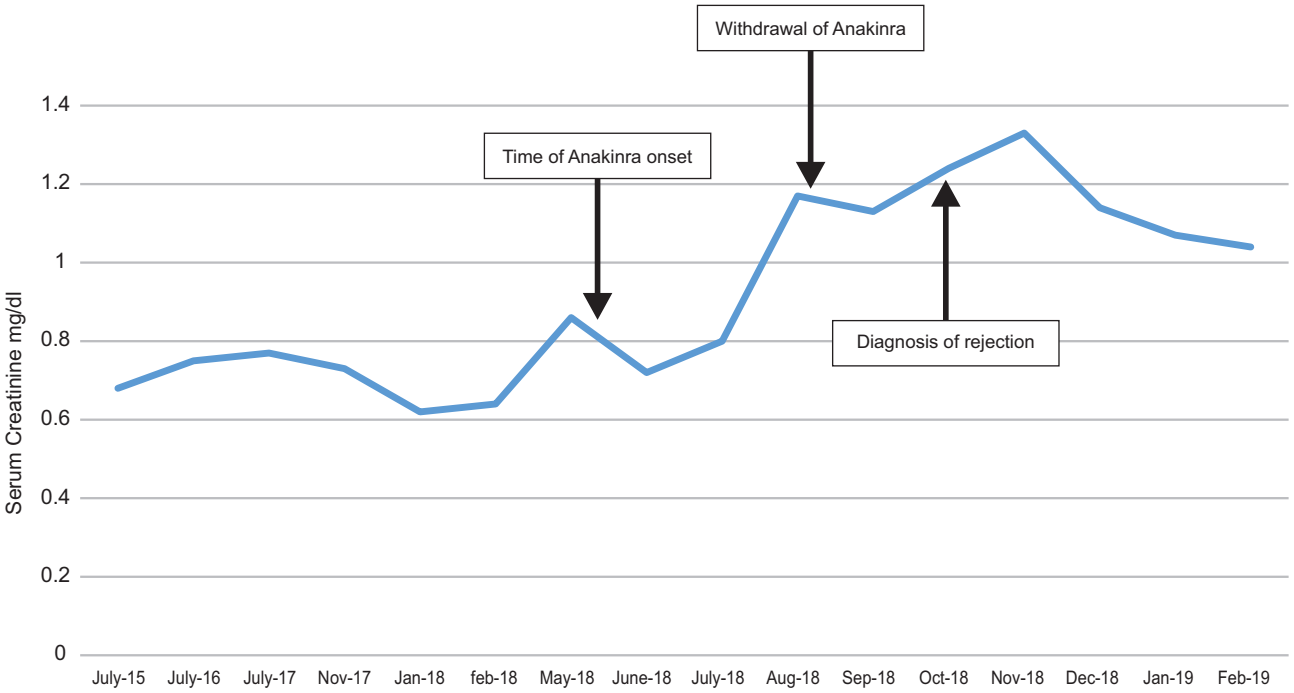
We present a 49-year-old woman who was diagnosed with AA type amyloidosis secondary to FMF at the age of twenty. Ten years after diagnosis, she started peritoneal dialysis as maintenance renal replacement therapy, and two years after the first transplantation was done from a living related donor. The patient lost his allograft due to hyper acute rejection. Then, she continued with peritoneal dialysis for seven years until the second kidney transplantation was done from a deceased donor. The patient and donor were one haplotype matched and class 1 and class 2 panel reactive antibodies were negative. Her allograft function was stable ten years after transplantation, and serum creatinine levels were between 0.6 to 0.8 mg/dL (Table). Anakinra treatment was started due to the resistant disease to colchicine. After eight months follow up there was no more attack of FMF, but a

Laboratory Parameters of the Patient Before and After Anakinra Treatment

Variables	Before Anakinra	After Anakinra (8th Month)	After Rejection Treatment
Hb, g/dL	14.9	12.6	12.3
WBC, 103 u/L	11.16	14.16	10.8
PLT, 109 u/L	364	422	378
BUN, mg/dL	14	38	27
Creatinine, mg/dL	0.64	1.36	1.04
eGFR, mL/m/ 1.73m^2	104.8	45.6	63
Sodium, mmol/L	139	139	138
Potassium, mmol/L	4.13	4.41	4.36
CRP, mg/L	23	7.8	1.18
24-h Urine Protein, mg/d	135	134	
Tacrolimus Level, ng/mL	5.6	5.7	7.5
BKV PCR	-	Negative	Negative
CMV PCR	-	Negative	Negative
Human Leukocyte Antigen			
A		24, 32	
B		52, 55	
DR		4, 11	

Hb, Hemoglobin; WBC, white blood cell; PLT, platelet; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.

moderate and persistent increase in serum creatinine level was observed (Figure). As the patient's creatinine level elevated simultaneously with the onset of Anakinra, treatment was discontinued, and other possible causes of allograft dysfunction were examined. Allograft biopsy was performed because renal doppler ultrasonography was within normal ranges and urine BK PCR, and CMV PCR were negative. Allograft biopsy was reported as acute T cell-mediated rejection compatible with BANFF type 2A. Methylprednisolone was started 500 mg/d for six days. Despite high dose glucocorticoid therapy, the creatinine level of the patient did not decrease; therefore anti-thymocyte



It shows serum Cr monitoring of the patient over time.

globulin (ATG) was initiated 2 mg/kg per dose for total dose of 10 mg/kg. After ATG treatment serum creatinine level decreased and stabilized to 1.04 mg/dL. Prednisolone dose was reduced to 5 mg gradually and the patient continued to use mycophenolate mofetil and tacrolimus as maintenance immunosuppressive therapy. The patient is still in follow up, and she is using colchicine for FMF. She experienced no FMF attack until now.

DISCUSSION

IL-1 blockade is an effective treatment option in patients with colchicine resistant FMF. To the best of our knowledge, there is no reported rejection episode associated with the use of Anakinra in the literature. Although, it is challenging to relate ACR episode directly to Anakinra use; the deterioration of allograft function, which has been stable for ten years until Anakinra usage and relatively late period for ACR development, makes the case interesting.

Two possible mechanisms could cause this association. One of these is that antibodies that develop against biological agents named as "anti-drug antibody" (ADA) may have triggered ACR. These antibodies are well defined and responsible for the non-response to biological agents and hypersensitivity reactions.[4] ADA development was defined against Infliximab, Etanercept, Canakinumab, Tocilizumab, and Anakinra in the literature.[5] ADA against biological drugs is strongly associated with T cell-dependent reaction lymphoid tissue, which requires CD40 and CD154 interaction. Therefore, antibodies against IL-1 receptor may facilitate the development of ACR by causing activation of T cells.

The other possible mechanism is the hapten induced rejection process. Haptens are small non-protein chemical groups, which could not cause antibody stimulation alone but gain antigenic structure when coupled to a carrier protein.[6] After binding to the carrier protein, they become immunogenic and can cross-link B cell receptors and activate T cells.[6] Also, there are immunogenetic factors defined that could facilitate hapten reactions such as HLA-B57, -B15, -B58, -DR4, and -DR2 alleles.[7,8] It has been shown that the risk of drug-related lupus development increases in the presence of these alleles.[7] Our patient may also be susceptible to hapten related reactions because of the presence of the HLA DR4 allele.

CONCLUSION

In conclusion, the possible role of Anakinra should be considered in cases of acute rejection of renal transplantation during the late period. Data about the possible side effects of biological agents in literature is growing. We informed a situation where we observed a possible relationship with the use of a biological agent in this report.

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REFERENCES

1. Meinzer U, Quartier P, Alexandra J-F, Hentgen V, Retornaz F, Koné-Paut I. Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. Semin Arthritis Rheum. 2011; 41:265-71.
2. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever: a survey of 470 cases and review of the literature. Am J Med. 1967; 43:227-53.
3. van der Hilst JC, Moutschen M, Messiaen PE, Lauwerys BR, Vanderschueren S. Efficacy of anti-IL-1 treatment in familial Mediterranean fever: a systematic review of the literature. Biologics. 2016; 10:75-80.
4. Doeleman MJ, van Maarseveen EM, Swart JF. Immunogenicity of biologic agents in juvenile idiopathic arthritis: a systematic review and meta-analysis. Rheumatology. 2019; 58(10):1839–1849.
5. Wikén M, Hallén B, Kullenberg T, Koskinen LO. Development and effect of antibodies to anakinra during treatment of severe CAPS: sub-analysis of a long-term safety and efficacy study. Clin Rheumatol. 2018; 37:3381-6.
6. Gefen T, Vaya J, Khatib S, et al. The effect of haptens on protein-carrier immunogenicity. Immunology. 2015; 144:116-26.
7. Dunphy J, Oliver M, Rands A, Lovell C, McHugh N. Antineutrophil cytoplasmic antibodies and HLA class II alleles in minocycline-induced lupus-like syndrome. Br J Dermatol. 2000; 142:461-7.
8. Yun J, Adam J, Yerly D, Pichler WJ. Human leukocyte antigens (HLA) associated drug hypersensitivity: consequences of drug binding to HLA. Allergy. 2012; 67:1338-46.

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