

Selective immunoglobulin A deficit in a haemodialysis patient
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To the Editor,

Selective deficit of immunoglobulin A (IgA) is one of the most common primary immunodeficiencies, and complicates the humoral defence system against infections that commonly enter the body via different mucous membranes. Its clinical spectrum is broad and ranges from nondescript symptoms (recurring ear, respiratory or gastrointestinal conditions) to severe invasive complications or even autoimmune disease (20%-30% of all cases). Another class of common manifestations in these patients are food allergies, asthma or post-transfusion allergies (10%-15% of the total).^{1,2}

In this singular pathogenic context (which has a variable incidence of 1:100-1:1000 individuals), we present the case of a 62-year-old patient with a history of advanced chronic kidney disease, who initiated urgent haemodialysis in the intensive care unit due to fluid overload, along with a cardiac tamponade that required evacuative pericardiocentesis. The patient's medical history included: high blood pressure, asymmetrical renal ultrasound (right kidney: 117mm vs left kidney: 96mm), atrial fibrillation, chronic degenerative vascular encephalopathy with long-term thalamic haematoma caused by anticoagulation with dicoumarin derivatives, monoclonal gammopathy with mild anaemia and thrombocytopenia, urticaria-angioedema with sensitivity to anisakis and intolerance to NSAIDs, recurrent respiratory infections with chronic bronchial disease, negative coagulopathy screening study, and unconfirmed findings of a weakly positive lupus anticoagulant. As for his clinical condition, uraemic symptoms upon hospitalisation – from the first dialysis session and despite meeting

the quality standards of the dialysis fluid (ultrapure water: <0.1CFU/ml, <0.03EU/ml endotoxin) – were accompanied by frequent episodes of hypersensitivity (HPS) type A in the form of hypotension and angioedema with poor response to prophylactic steroid therapy, changes in heparin prescription, dialyser change (polysulfone 1.8m² sterilised with in line steam, polyarylethersulfone-polyamide 2.1m² sterilised with gamma rays, polyacrylonitrile 2.15m² sterilised with gamma rays, heparinised Hephran 1.65m² sterilised with gamma rays, etc.) and even transition from on-line haemodiafiltration to high-flow haemodialysis. This simultaneously hindered giving appropriate renal replacement therapy, and constituted an obstacle to the recovery of the patient, which was delayed for several weeks.

The additional tests required for the evaluation of the overall process and HPS were:

- **Pre-dialysis biochemistry:** glucose: 70mg/dl; urea: 159mg/dl; creatinine: 7.9mg/dl; calcium: 8mg/dl; rheumatoid factor: 11.9IU/ml; total protein: 6.5g/dl; proteinuria in 24-hour urine sample: 835mg/l; and Bence-Jones proteinuria: negative.
- **Haemogram:** leukocytes: 10030/̄l (polymorphonuclear: 84.8%; lymphocytes: 6.6%; monocytes: 5.4%; eosinophils: 2%; basophils: 0.1%); haemoglobin: 8.6mg/dl (average cell volume: 91.7); platelets: 261,000/̄l; direct Coombs: negative.
- **Immunity:** antinuclear antibodies and antineutrophil cytoplasmic antibody: negative; C3/C4: 123/33.9mg/dl, lupus anticoagulant: (-).
- **Serology:** HbsAc-HbcAc: (+); hepatitis C virus: (-); human immunodeficiency virus: (-); negative syphilis.
- **Tumour markers:** negative.
- **Electrophoresis:** albumin: 52.1% (↑); gamma-globulins: 19.7% (↓);

albumin / globulin: 1.09%, with no monoclonal component.

- **Immunoglobulin:** IgG: 1412mg/dl; IgM: 121mg/dl; and IgA: 0mg/dl.

As to **specific allergy tests**, there was a very high total IgE (394KU/L), with negative tests for chloramines, latex of the extracorporeal circuit, and ethylene oxide/formaldehyde used as sterilisers.

Finally, and due to the suspected link between the allergic/thrombogenic tendency of the patient, the selective IgA humoral immunodeficiency and HPS manifested during dialysis, it was decided to also request specialised assessment from the haematology department, which excluded any spinal or immunological process different from that observed. However, ambulatory analysis of lymphocyte subpopulations provided new results: total lymphocyte count: 1172/̄l (0.9 to 5.2x10³/̄l); CD3-T: 889 cells/̄l 75% (58%-87%); CD3-CD4+: 52% (32%-62%); CD3-CD8+: 19% (12%-45%); CD4/CD8 ratio: 2.7 (0.8 to 4.5); CD19-B: 92 cells/ml 7% (7%-23%); and CD16-NK: 15% (4%-27%).

Thus, having excluded other causes of combined or secondary immunodeficiency, the final diagnosis was established: selective IgA deficiency linked to an allergic substrate with a tendency towards lymphocytopenia, normal CD4/CD8 ratio, and relative decline in B lymphocytes. The clinical expression of the patient's condition was not consistent with a reaction to latex, bio-incompatible membranes, or bradykinin release due to ethylene oxide.^{3,5} In contrast, its relationship with the IgE-mediated HPS was obvious. For that reason, the most plausible pathophysiological hypothesis for the manifestation of these symptoms was: 1) IgA deficiency caused initial antigenic overstimulation of CD4 T-cells, responsible for the activation of C3-CD8 and CD19-B lymphocytes, and as a result, the activation of cellular and humoral immunity⁶; 2) there was an abnormal maturation of B clones, responsible for the synthesis of IgA, hence the relative

deficit of CD19-B in our patient; however, this was not the case of other immunoglobulins such as IgE, which promote immediate mast cell degranulation when coming into contact with the antigenic factor^{7,8}; and 3) there was a tendency to develop infections and autoimmune mechanisms in these patients, where the uncontrolled external antigenaemia by IgA dimers was capable of inducing a direct cytotoxic response or a response mediated by Ag-Ac complexes.⁶

In this area of immunopathology, the proposed treatment was directed primarily at inhibiting the reaction of the extracorporeal blood-circuit interface, for which clinical experiences in the literature on pH-metric modulation of intradialytic anaphylaxis were reviewed.⁹ This was used to establish a screening protocol for patients with 1/6M-bicarbonate bloodlines (prior to connection during each session) resulting from the onset in an alkalinising effect that resolved the episodes of angioedema and haemodynamic instability. Secondly, we also adopted other therapeutic and hygiene measures for the prevention of infectious complications in the patient, such as the creation of an arteriovenous fistula, which was preferable over the central venous catheter that was being used, or even the early administration of antibiotic therapy in the case of respiratory infection. However, we did not consider correcting the IgA deficiency with exogenous immunotherapy, as severe cases of HPS secondary to the formation of anti-IgA antibodies have been described.¹⁰

Conflicts of interest

The authors declare no conflict of interest related to the content of this article.

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Severe levofloxacin-induced hypoglycaemia: a case report and literature review

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To the Editor,

We report a case of severe hypoglycaemia secondary to quinolones in a haemodialysis patient.

Our patient was a 72-year-old man who received haemodialysis three times a week with a tunnelled catheter. He was admitted for severe shivering during a dialysis session. Blood and catheter cultures showed *S. maltophilia* and *E. casseliflavus*. The catheter was removed, and antibiotic treatment was initiated with levofloxacin, at 250mg every 48h, and cotrimoxazole once a day.

The patient's renal failure was then treated medically. The sepsis developed without complication until the second week, when severe hypoglycaemia was detected, with neurological symptoms that persisted for three days. The patient received boluses of glucose at 30% via intravenous administration, and glucose infusion at 10%. Suspecting erroneous intake of oral hypoglycaemic agents, we performed a drug test but found no traces of these drugs. On the other hand, it did reveal the presence of toxic levels of levofloxacin.

The patient's underlying nephrological disease was a primary membranous glomerulopathy. The patient had been on haemodialysis for more than ten years, and had lost all arteriovenous fistulas. He also had undergone arthrodesis of the right knee, and had multiple infections of this joint. He was hypertensive, and did not suffer diabetes mellitus.

The patient was under normal treatment with water-soluble vitamins, amlodipine, and Venofer.