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CASE REPORT

Cutaneous allergic reaction correlates with anti-erythropoietin antibodies in dialysis patient developing pure red cell aplasia

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Abstract

We describe a case of concomitant erythropoietin allergy and resistance with a possible IgE and IgG-mediated immune response, in which the local allergic cutaneous symptoms preceded the antibody-mediated anemia.

KEYWORDS

allergy tests, anti-erythropoietin antibodies, erythropoetin allergy, pure red cell aplasia

1 | INTRODUCTION

Recombinant human erythropoietin (rhuEPO) is widely used for treatment of anemia associated to chronic kidney disease (CKD). Allergic reactions to rhuEPO and the development of anti-EPO antibodies are rare but severe side effects of rhuEPO treatment. Allergies to rhuEPO have been described but there are few data regarding the diagnosis by skin tests.[1] The allergic sensitization may be caused either by the rhuEPO or by the stabilizing agents.[2] Pure red cell aplasia (PRCA) is caused by EPO-neutralizing antibodies that antagonize both rhuEPO and endogenous EPO leading to severe anemia that paradoxically worsens with EPO therapy. PRCA is characterized by the absence of erythroid precursor cells in bone marrow samples, or maturational arrest of erythroid cells due to the absence of EPO activity, thus leading to rhuEPO resistance and progressive transfusion-dependent anemia.[3] Anti-EPO antibodies, first described in patients treated with epoetin alpha, cross-reacted with different rhuEPO.[4] A dramatic increase in PRCA has been reported since 1998, in coincidence with a change in the European epoetin alpha formulation: Human serum albumin, which acted as a stabilizer, was replaced with polysorbate 80. Thus, the

most likely hypothesis is that this change decreased the stability of the molecule and increased its immunogenicity,[5] especially for subcutaneous administration.[6] The incidence of PRCA later decreased after multiple safety interventions (reinforcement of cold storage chain, shift toward intravenous administration, and the elimination of uncoated rubber stoppers).[7] Nevertheless, new cases continue to emerge and the mechanism(s) responsible for the break in immune tolerance remains not completely understood.[8] There are few data about the clinical and laboratory response to the immunosuppressive therapy. Moreover, the role of allergic sensitization to rhuEPO in PRCA needs to be clarified.

2 | CASE HISTORY

A 41-year-old male with end-stage kidney disease on peritoneal dialysis and treated with rhuEPO developed cutaneous signs of allergy and subsequent severe anemia. After 5 months of subcutaneous therapy with epoetin zeta, the patient showed a local reaction of erythema and pruritic edema at the drug administration site. The cutaneous lesion was 10–15 cm in diameter and consistently occurred a couple of hours after injection. Symptoms regressed in a few days with topical steroids and systemic antihistamine medications. Epoetin zeta was initially substituted with darbepoetin alpha which caused even more pronounced skin reactions. Since the patient did not show any systemic symptoms, he continued the therapy with epoetin zeta and maintained stable hemoglobin (Hgb) levels. One year after starting rhuEPO therapy, Hgb suddenly decreased from 10–11 g/dl to 6.8 g/dl. At that moment, epoetin zeta was increased, from 4000 U/week to 8000 U twice/week, without any effect on Hgb values, reticulocytes count, and EPO blood level were low as well.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

Allergy skin tests confirmed positivity for different formulations of EPO and negativity for preservatives and concomitantly anti-EPO antibodies were detected by blood test. Allergy skin tests resulted positive with both epoietin zeta (3333 UI/ml—undiluted prick test negative, 0.2 ml intradermal test positive at a 1:10000 dilution) and darbepoetin alpha (500 mcg/ml—undiluted prick test 1/1 positive). Cutaneous test (prick test diluted sequentially to 1:10000, 1:1000, 1:100, 1:10, and 1:1) resulted all negative for polysorbate 20 (excipient of epoetin zeta) and polysorbate 80 (excipient of darbepoetin alpha). We also tested a long-acting formulation of epoetin beta (400 mcg/ml, excipient polietilenglicole) that resulted positive to undiluted prick test. We finally performed skin tests with the different epoetins and polysorbate in two healthy controls, with negative response.

After having excluded other potential causes of anemia, a diagnosis of PRCA was established on the basis of bone marrow aspiration and biopsy showing marked erythroid hypoplasia and the rhuEPO therapy was discontinued. The suspect of EPO resistance was further confirmed by positivity of anti-erythropoietin antibodies: ADA—anti-erytropoietin antibody titer >384 ng/ml (reference values <3 ng/ml) and NAB—neutralizing anti-erythropoietin antibody titer 1330 ng/ml (reference values <50 mg/ml) (QPS laboratories). During the following weeks, the patient required weekly red blood cells transfusions. Subsequently, the patient started 1 mg/kg daily oral prednisone therapy for 4 weeks, with subsequent tapering of the dose, followed by oral cyclosporine 3 mg/kg daily with a progressive resolution of anemia without any further need of transfusions; anti-EPO antibodies were again drawn after three months, with significant titer reduction.

4 | OUTCOME AND FOLLOW-UP

The patient underwent a functioning kidney graft in December 2019 preserving a stable Hgb under chronic immunosuppressive therapy with Tacrolimus, mycophenolate, and steroids. Our patient was not treated again with EPO; so, it remains uncertain whether this therapy can be resumed after the disappearance of antibodies. The trend over time of the Hgb and reticulocyte values, anti-EPO antibodies titer, and therapy variation is presented in Figure 1.

5 | DISCUSSION

To the best of our knowledge, this is the first case of EPO allergy, confirmed by allergy tests, preceding PRCA as possible consequence of a double and sequential IgE and IgG-mediated immune response, in which the local cutaneous reaction anticipated the antibody-mediated anemia. The local cutaneous reaction to rhuEPO, is probably caused by an IgE mechanism, cross- reactive with all epoetin formulations, as shown by the positivity of cutaneous allergy tests with 3 different epoetins formulation and the negativity to stabilizing agents. However, the formulation without preservatives is not available as a proof of concept. The development of EPO resistance causing PRCA and the demonstration of anti-EPO antibodies suggested an IgG-mediated mechanism that was confirmed

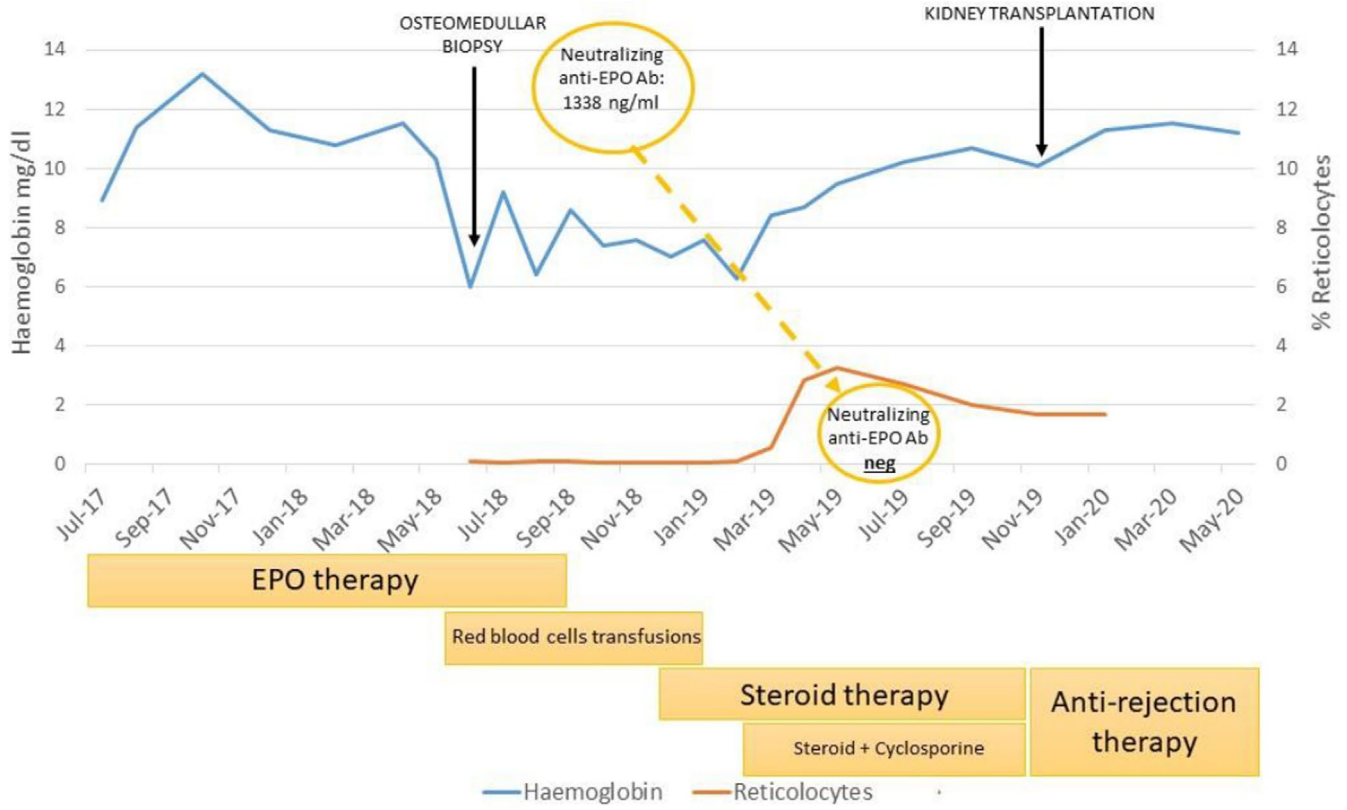

FIGURE 1 Trend over time of the hemoglobin values (mg/ml), percentage of reticulocytes, anti-EPO antibodies titer, and therapy variation

by a high titer of neutralizing antibodies.[9] Other authors noted that all patients who develop EPO antibodies received subcutaneous rhuEPO and hypothesized that the administration route may increase drug immunogenicity.[4] Immunosuppressive therapy was successfully used, the patient did not develop any infectious complication during the cyclosporine course, and he was able to successfully continue peritoneal dialysis. Cessation of EPO exposure and immunosuppressive therapy was effective in this clinical case.

Whether the IgE-mediated reactions correlated or were causative of the development of the red cell aplasia is far from clear. However, the sudden appearance of severe and persistent anemia in patients receiving rhuEPO should suggest the need for immediate screening for anti-EPO antibodies. We herein highlight that local drug reactions could be an alarm for the subsequent development of severe anemia. Allergy skin tests can help to identify EPO allergies in a quick and reproducible manner, but requires well-trained personnel for the execution and interpretation of diagnostic tests. Testing for the preservative is also advised to rule out a confounding factor. On the contrary, serological testing of anti-EPO antibodies for the diagnosis of PRCA is not routinely available in most clinical laboratories.

Therefore, the detection of positive allergy tests to EPO in patients with local skin reactions and persistent anemia could be a warning sign for the development of anti-EPO antibodies, should suggest carrying out serological tests and could facilitate the recognition of patients at risk to develop PRCA and a promptly cessation of treatment with EPO.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Iuliana Badiu, Davide Diena, Giuseppe Guida, Carlo Ferrando, Davide Rapezzi, and Luca Besso participated to the diagnosis and therapy of the patient, wrote the manuscript, read and approved the final manuscript.

ETHICAL APPROVAL

The research was conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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