

Additionally, this was a retrospective review and only one of the three subjects was evaluated by a consulting dermatologist. While oncologists and other health care providers may routinely evaluate skin eruptions in HSCT patients, clinical assessment by an experienced dermatologist remains the standard of care at most centres.

Transfer of atopy and contact allergy from donor to recipient following bone marrow transplantation has been described,^{5,6} and the presumed mechanism is via adoptive transfer of donor memory T cells to a newly reconstituted recipient immune system. There is also evidence of allergen-specific IgE-mediated hypersensitivity passed from donors to recipients of stem cell transplantation via B cell transfer.⁷ Thus, HSCT may predispose certain patients to the development of atopy or new environmental and medication allergies.

Whether drug allergies persist in patients undergoing non-myeloablative HSCT or in HSCT recipients with less than total donor chimerism is unknown, and there are no published data on drug allergy persistence following HSCT.

This observational study suggests that there may be an important immunologic component of drug allergy that may influence the development of acute GVHD. A prospective multi-centred trial with dermatologist evaluation of skin eruptions in HSCT patients would help to further elucidate both the role of medication allergy as a risk factor for GVHD and the presence or absence of drug allergy following transplant.

Ethical disclosures

Protection of human subjects. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

This research was supported in part by NIH grants 3R01CA125077-01A1 (D.P.W.) and 3R01CA125077-01A1S1 (D.P.W.). Dr. Cotliar is supported by a career development award from the Dermatology Foundation.

References

- Horn TD, Redd JV, Karp JE, Beschorner WE, Burke PJ, Hood AF. Cutaneous eruptions of lymphocyte recovery. *Arch Dermatol.* 1989;125:1512–7.
- Bolognia JL, Cooper DL, Glusac EJ. Toxic erythema of chemotherapy: a useful clinical term. *J Am Acad Dermatol.* 2008;59:524–9.
- Conlon JD, Dauenhauer M, Tonkovic-Capin V, Talano J, Margolis D, Drolet BA, et al. Voriconazole-induced blistering in the setting of graft versus host disease: a report of 2 patients. *J Am Acad Dermatol.* 2008;58:484–7 [Case Reports].
- Au WY. Relevance of drug allergy history after allogeneic hemopoietic stem cell transplantation. *Bone Marrow Transplant.* 2007;40:179–80 [Research Support, Non-U.S. Gov't].
- Bellou A, Kanny G, Fremont S, Moneret-Vautrin DA. Transfer of atopy following bone marrow transplantation. *Ann Allergy Asthma Immunol.* 1997;78:513–6 [Case Reports].
- Olaguibel J, Almodovar A, Giner A, Serrano G, Martinez J, Basomba A. Passive transfer of contact sensitivity to colophony as a complication of an allogeneic bone-marrow transplant. *Contact Dermatitis.* 1989;20:182–4 [Case Reports].
- Agosti JM, Sprenger JD, Lum LG, Witherspoon RP, Fisher LD, Storb R, et al. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med.* 1988;319:1623–8 [Research Support, U.S. Gov't, P.H.S.].

J. Gordon^a, E. Damstetter^a, B. Nardone^a, J. Mehta^{b,c}, D.P. West^{a,c}, J. Cotliar^{a,c,*}

^a Department of Dermatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

^b Department of Medicine, Division of Hematology/Oncology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

^c Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

*Corresponding author.

E-mail address: j-cotliar@northwestern.edu (J. Cotliar).

<http://dx.doi.org/10.1016/j.aller.2013.01.006>

Adverse reaction after administration of progesterone

To the Editor,

Progesterone is a hormone that inhibits contractions of uterus, facilitates the implantation of the embryo and maintains the pregnancy. In the pregnant uterus, progesterone plays a role in controlling the development of endometrial receptivity and in the processes of an angiogenesis and trophoblast invasion.^{1,2}

An inadequate secretion of progestogens in the early phases of pregnancy seems to be related to many cases of miscarriage. Therefore, a progesterone supplementation therapy has been used to prevent spontaneous pregnancy loss and also to prevent the preterm birth.³ There is some evidence, too, to indicate that women with idiopathic recurrent miscarriage may benefit from the immunomodulatory properties of progesterone in early pregnancy.⁴ In some cases vaginal progesterone therapy has been demonstrated effective to reduce the risk of miscarriage and without important side effects.⁵ However, until now there has been

uncertainty about the real utility of routine use of progestogens to prevent miscarriage in pregnancy.⁶

We report a case of a 23-year-old Caucasian woman, with no significant past medical history, admitted to our Division of Allergy and Clinical Immunology, referring to an adverse reaction which occurred during the 9th week of her first pregnancy, to progesterone administered to prevent miscarriage. She had never before taken estroprogestins. She reported that after 2 h of intravaginal administration of 100 mg of progesterone, labial and hands angio-oedema appeared. Twenty-four hours after progesterone treatment, miscarriage occurred. Thus she underwent uterine curettage intervention, performed under general anaesthesia induced by administration of propofol and fentanyl. Before surgery she underwent premedication protocol, as indicated from "Memorandum SIAIC (Italian Society of Allergology and Clinical Immunology) on the diagnosis of allergy/intolerance to drugs". Premedication consists of the administration of prednisone 13 h, 7 h and 1 h associated to the intramuscular administration of chlorpheniramine maleate 1 h before surgery.⁷ When the woman came to our observation, after a physical examination which did not show any remarkable abnormality, a challenge test for the progesterone derivative hydroxyprogesterone was performed, with a positive result (a wide itching wheal) 3 h after the intradermal injection of the undiluted drug. The tolerance test for the alternative medication is a procedure characterised by intradermal injection of scalar dilutions of the drug, followed by the administration of the whole dose of the drug.⁸

There are several data supporting the effective use of progesterone to prevent spontaneous miscarriage.⁹ We retain this case of interest because miscarriage, this time, seems to be a consequence of administration of progesterone.

To evaluate the causality connection between the adverse reaction and progesterone administration we applied the Naranjo adverse drug reaction probability scale.¹⁰ This algorithm permits to assign the likelihood of a drug to be the cause of an unexpected event. Through a ten-item questionnaire it assigns numerical values to arrive at an overall total score for probability assignment. Depending on the score obtained, the causality connection may be indicated as certain, probable, possible, unlikely. The total score of our case was 6, so the causality connection can be considered probable.

Hypersensitivity to progesterone is a rare clinical condition in which patients display hyper-sensitivity to endogenous or exogenous progesterone. It seems to occur as the result of an autoimmune response to endogenous progesterone production but can also be caused by exogenous intake of a synthetic progestin. This disorder has been reported to occur during pregnancy, in the postpartum period, in post-menopausal women taking hormone replacement therapy, and even in men taking exogenous synthetic progesterone.^{11,12}

The relationship between progesterone activity and the immune system has been investigated. Peripheral blood gamma delta T cells of pregnant women and peripheral natural killer cells express lymphocyte progesterone receptors. This recognition of foetal antigens is required for the initiation of progesterone-dependent immunoregulatory mechanisms.¹ Quite uncommon progestin-induced

side effects are hypersensitivity reactions. Cases of autoimmune progesterone anaphylaxis and dermatitis, due both to an autoimmune reaction to endogenous progesterone production, and to exogenous intake of a synthetic progestogen, have been reported. Moreover, progesterone-induced urticaria has also been described.¹³⁻¹⁵ However, progesterone seems to have a discrepant action because even if it contributes in suppressing the histamine release, still it can cause potentiation of the IgE formation.¹⁶ The risk profile of progestogens is characterised by non-specific reported adverse effects (with incidence rates between 1% and 10%) common to substances belonging to this class of drugs. The most frequently-reported adverse effects are bleeding problems, headache, breast and pelvic pain, altered or depressed mood, nausea, acne and weight gain.¹⁷

In conclusion, we report a case of miscarriage probably caused by a hypersensitivity reaction to progesterone in a woman whose anamnesis revealed a link between the appearance of symptoms and the timing of the event. Successively, a positive response to an intradermal test with progesterone derivative hydroxyprogesterone was demonstrated. In the light of the common use of progesterone supplementation therapy to prevent spontaneous abortion and preterm birth and according to the possibility of occurrence of hypersensitivity reactions to progestogens, we suggest to evaluate the opportunity to ascertain this individual predisposition in pregnant.

Ethical disclosures

Protection of human subjects and animals in research.

The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Szekeres-Bartho J. Progesterone-mediated immunomodulation in pregnancy: its relevance to leukocyte immunotherapy of recurrent miscarriage. *Immunotherapy*. 2009;1:873-82.
2. Nardo LG, Sallam HN. Progesterone supplementation to prevent recurrent miscarriage and to reduce implantation failure in assisted reproduction cycles. *Reprod Biomed Online*. 2006;13:47-57.
3. Dodd JM, Crowther CA, Cincotta R, Flenady V, Robinson JS. Progesterone supplementation for preventing preterm birth: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2005;84:526-33.
4. Di Renzo GC, Giardina I, Clerici G, Mattei A, Alajmi AH, Gerli S. The role of progesterone in maternal and fetal medicine. *Gynecol Endocrinol*. 2012;28:925-32.

5. Check JH. A practical approach to the prevention of miscarriage. Part 1 – progesterone therapy. *Clin Exp Obstet Gynecol*. 2009;36:203–8.
6. Haas DM, Ramsey PS. Progesterone for preventing miscarriage. *Cochrane Database Syst Rev*. 2008;16:CD003511.
7. Memorandum SIAIC (Italian Society of Allergology and Clinical Immunology) on the diagnosis of allergy/intolerance to drugs; 1998.
8. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy*. 2003;58:854–63.
9. Wahabi HA, Fayed AA, Esmail SA, Al Zeidan RA. Progesterone for treating threatened miscarriage. *Cochrane Database Syst Rev*. 2011;7:CD005943.
10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–45.
11. Stranahan D, Rausch D, Deng A, Gaspari A. The role of intradermal skin testing and patch testing in the diagnosis of autoimmune progesterone dermatitis. *Dermatitis*. 2006;17:39–42.
12. Herzberg A, Strohmeyer C, Cirillo-Hyland V. Autoimmune progesterone dermatitis. *J Am Acad Dermatol*. 1995;32:333–8.
13. Magen E, Feldman V. Autoimmune progesterone anaphylaxis in a 24 year old woman. *Isr Med Assoc J*. 2012;14:518–9.
14. George R, Badawy SZ. Autoimmune progesterone dermatitis: a case report. *Case Rep Obstet Gynecol*. 2012;2012:757854.
15. Bernstein IL, Bernstein DI, Lummus ZL, Bernstein JA. A case of progesterone-induced anaphylaxis, cyclic urticaria/angioedema, and autoimmune dermatitis. *J Womens Health (Larchmt)*. 2011;20:643–8.
16. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy*. 2008;63:1418–27.
17. Ruan X, Seeger H, Mueck AO. The pharmacology of nomegestrol acetate. *Maturitas*. 2012;71:345–53.

G. Calapai^a, S. Imbesi^{b,*}, M. Miroddi^a, S. Isola^b,
L. Venuto^b, M. Navarra^c, S. Gangemi^b

^a Department of Clinical and Experimental Medicine and Pharmacology, Section of Pharmacology, University of Messina, Messina, Italy

^b Department of Clinical and Experimental Medicine, School and Unit of Allergy and Clinical Immunology, University of Messina, Messina, Italy

^c Pharmaco-Biological Department, University of Messina, Messina, Italy

*Corresponding author.

E-mail address: sele19pf@gmail.com (S. Imbesi).

<http://dx.doi.org/10.1016/j.aller.2013.02.005>

Non-Hodgkin's lymphoma in a patient with leucocyte adhesion deficiency

To the Editor,

Leucocyte adhesion deficiency type 1 (LAD-1) is a rare autosomal recessive primary immunodeficiency disorder, characterised by the absence or deficient expression of the adhesion molecules on leucocytes. The disease is usually associated with leucocytosis, recurrent severe bacterial and fungal infections without pus formation and impaired wound healing. Omphalitis, delayed umbilical cord separation, perirectal abscess, sepsis, necrotising enterocolitis, pneumonia, gingivitis and periodontitis are common features of disease.^{1–3} Although some forms of primary immunodeficiency diseases could develop malignancies, there is no report of non-Hodgkin's lymphoma in patients with LAD.

Herein a boy is presented who was admitted to the NICU ward because of omphalitis, sepsis, icterus and erythematous rashes. He was the second child of consanguineous parents. The first child of the family was a girl who died at three months of age due to pneumonia. The culture of umbilical discharge of the patient was *Pseudomonas* spp. While he was receiving treatment, he developed right foot cellulites. Radioisotope scanning showed arthritis in right knee. His umbilical cord had been cut on 32 days of life. Lab data revealed leucocytosis 30,000/mm³ with neutrophilia (65%) and eosinophilia (10%). Serum immunoglobulin (Ig)G, IgM, IgA, and NBT tests were all normal. Peripheral blood flow cytometric analysis revealed normal T-, B- and NK

cell numbers, but was compatible with LAD-1 (CD18 = 0.5%, CD11a = 0.5%, CD11b = 0%, CD11c = 1.2%). He had history of several episodes of sepsis, pneumonia, diarrhoea, typhlitis, necrotic skin ulcers and infections because of *Pseudomonas* spp. and *S. aureus* after diagnosis.

The 3rd sibling of this family is a girl, who was admitted to the NICU at age of 30 days because of delayed separation of umbilical cord and omphalitis. Her laboratory data revealed leucocytosis (27,000/mm³) with neutrophilia (82%). Serum immunoglobulins and NBT were normal. Chemotaxis was impaired and peripheral blood flow cytometric analysis revealed low expression of CD18 (CD18 = 1.6%, CD11a = 0.2%, CD11b = 1.0%, CD11c = 5%). T-, B- and NK subpopulation numbers were normal. Now, she is six years old and has undergone recurrent severe diarrhoea, pneumonia, skin infections with necrotic ulcers due to *Pseudomonas* spp. and *S. aureus*, chronic gingivitis and chronic otitis media with discharge. Both siblings have failure to thrive.

During follow-up, the boy was admitted into the hospital due to abdominal mass at the age of seven years. The mass (3 cm × 4 cm) removed in appendix with partial residue in ileocecal region during laparotomy. Pathology reported diffuse large B-cell lymphoma as a primary tumour in the abdomen being positive for CD20 and CD22. Genetic evaluation showed *t* (8:14) in mass. Other investigation to determine the clinical extent of the disease for staging showed stage II of disease. He received LMB-96 protocol. During chemotherapy, he had several episodes of severe infection and abscess formation. The result of treatment was excellent after treatment and now he is alive, 11 years old, without any recurrence of disease.