Documented exogenous progesterone hypersensitivity related to the use of combined oral contraceptive

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DESCRIPTION

An 18-year-old woman with medical history of asthma reported a maculopapular non-pruritic rash on her neck and chest, throat closing sensation and chest tightness after 6 weeks of treatment with a combined oral contraceptive pill (OCP) ordered by her gynaecologist. The medication contained ferrous fumarate, ethinyl estradiol, and norethindrone acetate. Symptoms resolved within 3 days of discontinuation of the OCP and treatment with diphenhydramine.

At evaluation, physical examination was noncontributory. There was no evidence of eosinophilia on laboratory work up. Skin testing for the different components of the medication was performed with previous reported non-irritant concentrations¹ (skin prick testing (SPT) and intradermal (ID)): progesterone 50 mg/mL (SPT undiluted; ID 1: 10 000, 1: 1000, 1: 100), estradiol 25 mg/mL (SPT undiluted; ID 1: 10 000, 1: 1000, 1: 100), ferrous sulfate 60 mg/mL (SPT undiluted; ID 1: 1000, 1: 100, 1: 10) and OCP dissolved in 1 mL (SPT undiluted; ID 1: 1000, 1: 100, 1: 10). Both progesterone and estradiol were diluted in olive oil based on a previous report by Foer *et al.*¹ Ferrous sulfate and the OCP were diluted in human serum albumin (HSA) and filtered through a 0.22 µm filter. Histamine diphosphate 1 mg/mL and HSA were used as positive and negative controls, respectively.

Skin testing was positive for progesterone (ID (0.005 mg/mL)), ferrous fumarate (ID (6 mg/mL)) and combined OCP (ID (pill dissolved in 1 mL); figure 1). The patient was advised to avoid these medications and use estrogen-only contraceptive methods. The patient has been symptom-free since she suspended the combined OCP. Four months later, the patient was required to start iron replacement therapy due to anaemia. An open oral graded challenge to iron-containing multivitamin was performed without adverse reactions.

Progesterone hypersensitivity (PH) is a rare condition that occurs in women of childbearing age.² It has a diverse clinical presentation with symptoms including rash, urticaria with or without angioedema, wheezing, shortness of breath and anaphylaxis but can also present with erythema multiforme, fixed drug eruption and vesicular and bullous eruptions.³ PH can be secondary to endogenous or exogenous sources of progesterone. Exogenous sources of progesterone include oral and implantable contraceptives, long-acting depot

preparations, emergency contraception and intra-uterine devices; they are an important and growing consideration in diagnosing PH, especially with the increasing use in contraceptive methods and in vitro fertilisation (IVF).¹

While it is more common to develop hypersensitivity reactions after IVF, considering the high levels of progesterone required, reactions to OCPs are more uncommon in view of the lower progesterone doses they contain. OCPs are usually found to be the primary source of exposure to progesterone in patients with endogenous PH. In a report of 24 PH cases, 58% of the patients presented symptoms after previous exposure to exogenous progesterone, and 25% were specifically secondary to OCP exposure.¹

Diagnosing PH may be challenging due to its diverse clinical presentation. In this case, the diagnosis was based on the correlation of symptoms with the use of an OCP and was confirmed with skin testing. A positive skin test proves the sensitivity to progesterone, but a negative result does not rule out the diagnosis. Immunological tests

Figure 1 Testing for the different components of the medication. Positive progesterone testing (10 mm×no flare), ferrous (11.5×17.5 mm) and diluted OCP (6×12.5 mm) with a positive histamine control (10×25 mm). Negative oestrogen and negative control. HSA, human serum albumin; OCP, oral contraceptive pill.

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such as progesterone-specific IgE or basophil activation testing are possible diagnostic tests, which need to be studied further.

Learning points

- ▶ Exogenous sources of progesterone are an increasing cause of progesterone hypersensitivity.
- ▶ Oral contraceptive pills are usually found to be the primary source of exposure to progesterone in patients with exogenous progesterone hypersensitivity.
- ▶ Diagnosing progesterone hypersensitivity may be challenging, but the combination of clinical history with a positive skin testing confirms the diagnosis.

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manuscript. DAH analysed and interpreted the data and prepared the manuscript. AG-E contributed to conception and design, did supervision, analysed and interpreted the data and prepared and critically revised the manuscript.

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