Successful assisted conception in a case of recalcitrant chronic urticaria treated with omalizumab: a case report

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SUMMARY

Chronic urticaria (CU) is a debilitating disease characterized by recurrent wheals, angioedema, or both, lasting for at least six weeks. Although self-limiting, it remains a challenging condition to manage, particularly in patients with specific comorbidities. We report the case of a 39-year-old woman with recalcitrant CU and polycystic ovarian syndrome (PCOS), along with a history of adverse obstetric events. Her CU was successfully treated with subcutaneous omalizumab, providing excellent symptom control and enhancing her quality of life. Subsequently, she underwent an uneventful assisted reproduction technology (ART) procedure with a meticulously timed, resulting in the birth of healthy twins. This case highlights the role of omalizumab in treating recalcitrant CU during the preconception period and its continuation throughout pregnancy. It also underscores the importance of a comprehensive multidisciplinary approach in achieving a successful outcome.

INTRODUCTION

Chronic urticaria presents as recurrent episodes of wheals, angioedema, or both, persisting for at least six weeks. CU can be classified into either spontaneous or inducible forms. This condition is driven by mast cells, whose activation triggers the release of histamines and cytokines, leading to sensory nerve activation, vasodilation, and plasma extravasation. Globally, the point prevalence of CU is estimated to range from 0.1% to just under 1%.[1] As CU significantly affects a patient's quality of life, the Urticaria Activity Score 7 (UAS7) serves as a valuable tool for evaluating disease severity based on daily symptoms over the past seven days. A UAS7 score below 7 indicates well-controlled urticaria.[2]

CASE PRESENTATION

A 39-year-old woman with a history of three miscarriages and no living child was under follow-up at an Infertility Clinic since her last spontaneous miscarriage in 2013. She was diagnosed with polycystic ovarian syndrome (PCOS) based on her irregular anovulatory cycles and polycystic ovaries observed on transvaginal ultrasound. She had chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) for the past 14 years, with wheals occurring spontaneously, over areas with sustained pressure (delayed pressure urticaria), and after exercising (cholinergic urticaria). Notably, she was labeled allergic to ibuprofen, mefenamic acid, metronidazole, ciprofloxacin, azithromycin, metoprolol, prazosin, perindopril, amlodipine, tranexamic acid, and micronized progesterone due to coincidental wheals appearing when those medications were initiated. She was treated with second-generation H1 antihistamines (SgAH) under dermatology follow-up for the past year. Her chronic urticaria was initially managed with SgAH at a twofold standard dose, which was then increased to a fourfold dose.

Over two years, she underwent two cycles of intrauterine insemination (IUI). The first IUI cycle was performed with clomiphene citrate but was unsuccessful despite a good follicular response. During her second IUI attempt using clomiphene citrate and low-dose gonadotropin, she developed multiple follicles, leading to the procedure being converted to in-vitro fertilization (IVF). She developed breathlessness and chest pain five days after ovum retrieval. Her cardiac enzymes, electrocardiogram, and echocardiogram were normal. A computed tomography pulmonary angiography (CTPA) showed no evidence of pulmonary embolism, but it revealed mild cardiomegaly and mild pleural effusion (Figure 1). She was diagnosed with moderate to severe ovarian hyperstimulation syndrome (OHSS). She also experienced worsening urticaria, along with vomiting and abdominal pain, occurring within several hours to days after each assisted reproductive treatment. A dermatology consult was sought for treatment optimization before proceeding with further fertility treatment.

In 2018, her Urticaria Activity Score 7 (UAS7) ranged from 16 to 18 (Figure 2) despite the addition of montelukast; therefore, oral cyclosporin was initiated. Her UAS7 remained unchanged while on cyclosporin at 2.5 mg/kg/day. After two months, cyclosporin was discontinued as she developed peripheral numbness. She was started on subcutaneous omalizumab 300 mg in March 2019. After three weeks of treatment, her UAS7 score dropped to 7 (Figure 2). She experienced a headache after the injection; thus, the dose was reduced to 150 mg every four weeks.

Three months after starting omalizumab, she underwent frozen embryo transfer (FET). An artificial cycle using

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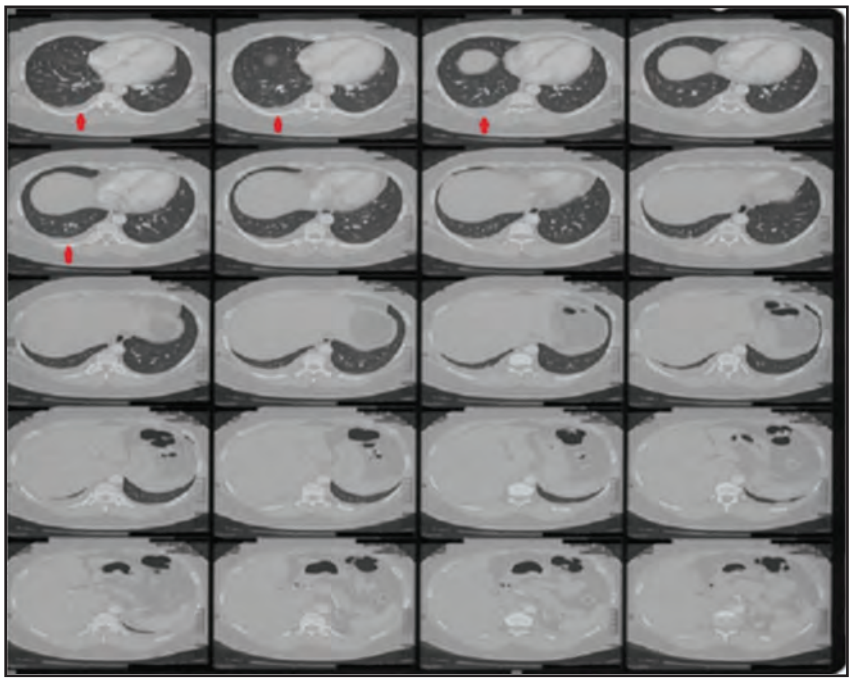

Fig. 1: Mild pleural effusions detected in the right lung base (indicated by red arrow)

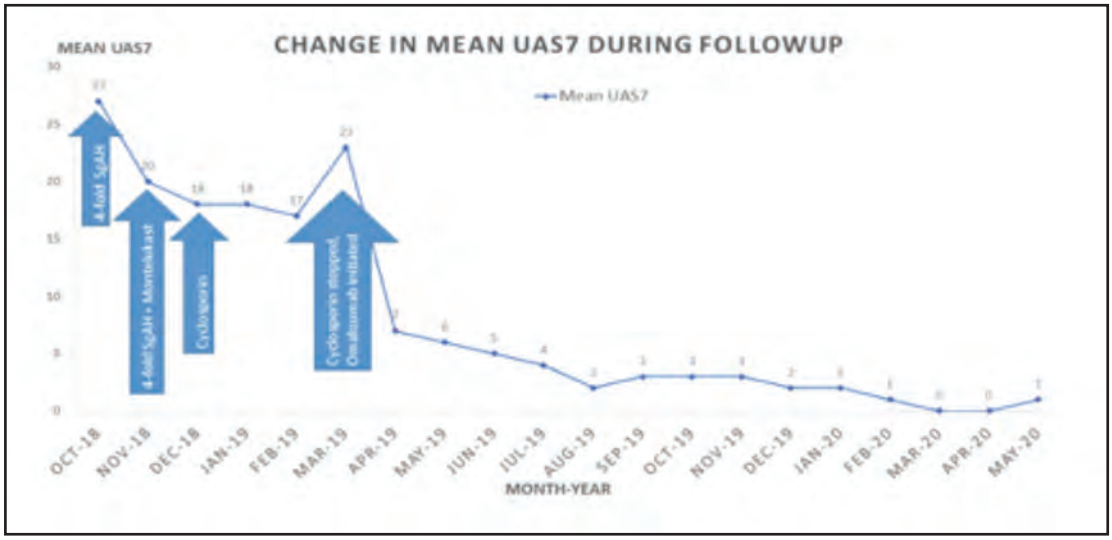

Fig. 2: showed reduction in the patient's UAS7 score chart after omalizumab initiated

estradiol valerate 4 mg twice daily was initiated. By day 10 of the cycle, her endometrial lining measured 8 mm and displayed a trilaminar pattern. On the day of transfer, two of her embryos had proliferated to more than 10 cells, and one had developed early compaction features. She experienced nausea and urticaria after the procedure. Her serum tryptase levels were normal. Two weeks after the embryo transfer, her serum βhCG level was 925 IU/L, and the subsequent ultrasound confirmed the presence of two gestational sacs (Figure 3).

She was closely monitored by the maternal-fetal medicine team throughout the antenatal period. Monthly subcutaneous omalizumab at 150 mg was continued with good efficacy. Both twins were growing appropriately for gestational age. At 34 weeks of gestation, she went into preterm labour and underwent an emergency Lower Segment Caesarean Section (LSCS). She breastfed both her babies, who remained well until one month of age with no evidence of neonatal thrombocytopenia.

DISCUSSION

OHSS is a complication of controlled ovarian hyperstimulation. The pathogenesis of OHSS involves the shift of fluid from the intravascular compartment into the third space. Various theories explain the development of OHSS. The first is the role of vascular endothelial growth

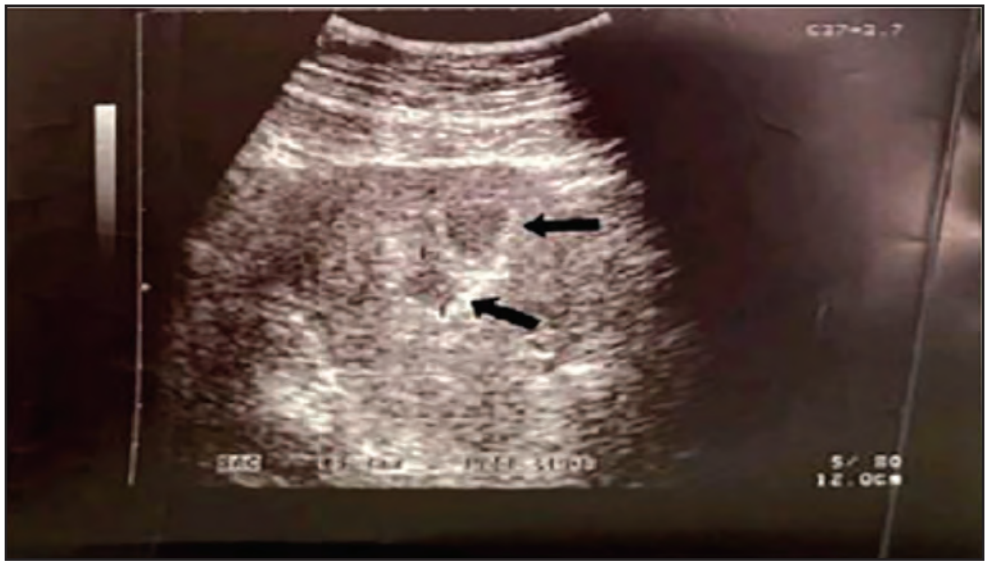

Fig. 3: Ultrasound showed presence of two gestational sacs indicating twin pregnancy

factors (VEGF), which mediate capillary permeability and increase the risk of ascites. Another theory involves interleukin 6 (IL-6), which has been found to be elevated in cases of OHSS.[3]

Our patient had CSU with concomitant inducible urticaria since the age of 25, with varying disease severity. It has been reported that delayed pressure urticaria occurs in 10% to 50% of patients with CSU, often presenting with greater severity and a longer duration of illness.[4,5] She was classified as allergic to multiple medications, likely due to the appearance of wheals that coincided with medication use. She had poorly controlled CSU and physical urticaria.

As our patient was refractory to SgAH at four times the standard dose, montelukast, and cyclosporin, she was initiated on omalizumab for CSU management. Omalizumab is a recombinant monoclonal anti-IgE antibody approved for the treatment of chronic urticaria unresponsive to SgAH.[1] Omalizumab binds to the Fc portion of immunoglobulin E (IgE), preventing IgE from binding to its receptor, FcεRI. This leads to a significant reduction in serum-free IgE. Additionally, there is a downregulation of FcεRI.[6]

Omalizumab has not been approved for CSU treatment during pregnancy, despite being assigned a Pregnancy Category B rating by the FDA.[7] An editorial reported that omalizumab, an IgG antibody, is transferred to the baby via the placenta, with the greatest exposure occurring in the third trimester.[8] Moreover, IgG complexes are transferred through neonatal Fc receptor-mediated transcytosis.

The largest published study on the safety of omalizumab in pregnancy is the expect study, in which 250 pregnant women with asthma received at least one dose of omalizumab within 8 weeks before conception or at any time during pregnancy. There was no increased prevalence of major congenital anomalies, prematurity, or small-for-gestational-age infants compared to pregnant women with asthma who were not exposed to omalizumab. Furthermore, no increased risk of neonatal thrombocytopenia was found in the cohort, a concern previously reported in non-human primates.[7]

To date, several case reports have documented the use of omalizumab in pregnancy for CSU with favourable outcomes. However, data on omalizumab use for CIndU remain limited, as these patients were excluded from randomised controlled trials of omalizumab. Nonetheless, there is growing evidence that both CSU and CIndU can be successfully treated with omalizumab.[5]

Furthermore, Vieira dos Santos et al. reported a case of a pregnant woman with CSU and CIndU (pressure urticaria and dermographism) who was effectively treated with omalizumab, highlighting its similar mechanism of action across urticaria subtypes.[9] Liao et al. reported two cases in which patients became spontaneously pregnant while receiving omalizumab for CSU. One patient was exposed to omalizumab at 300 mg every four weeks for two months and was later found to be 10 weeks pregnant at a follow-up visit. The other patient conceived three months after being treated with omalizumab, and both were reported to be well without complications.[10]

Although most cases support the use of omalizumab in pregnancy and its safety, further research is needed.

To our knowledge, this is likely the first case to describe the use of omalizumab for CU in conjunction with FET as part of ART in a patient with infertility, PCOS, and recurrent miscarriage.

CONCLUSION

Omalizumab has a good safety profile and is effective for refractory CU. Therefore, it should be considered a treatment option for pregnant women with this condition. Further studies are needed, particularly to evaluate its long-term safety, efficacy, and effects when used during the periconceptional period.

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