RELATIONSHIP BETWEEN CYTOKINES IN ASCITES AND THE SEVERITY OF OVARIAN HYPERSTIMULATION SYNDROME: A CASE REPORT

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SUMMARY

Objective: Determination of the correlation of interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF) levels in serum and ascites with the severity of ovarian hyperstimulation syndrome (OHSS).

Case Report: We present the case of a woman with primary infertility who was enrolled in an ovulation induction program. OHSS developed 6 days after artificial insemination with the husband’s sperm. We performed continuous paracentesis and recorded daily concentrations of IL-1, IL-6, IL-8, TNF, and VEGF in serum and ascites in an attempt to determine their correlation with the severity of OHSS.

Conclusions: Improvement in symptoms and a decreasing amount of ascites were correlated with a decreasing serum concentration of VEGF.

Key Words: ovarian hyperstimulation syndrome, interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor, vascular endothelial growth factor

Introduction

Assisted reproductive techniques are well established in overcoming the increasing problem of infertility. Unfortunately, a serious and potentially life-threatening complication, ovarian hyperstimulation syndrome (OHSS), sometimes occurs due to ovulation induction. The incidence of OHSS in in vitro fertilization programs is approximately 1–10% of induced cycles [1]. Severe forms of OHSS occur in 0.5% of patients [2]. Although the pathophysiology of this syndrome has not been completely elucidated, many of the clinical manifestations of OHSS resemble a noninfectious systemic inflammatory response, characterized by increased vascular permeability, hypotension, and shock, progressing to intravascular depletion, renal failure, and death. During the last decade, several studies have reported that levels of many cytokines, including interleukin (IL)-6, IL-8, tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF), are correlated to this syndrome [3]. Whether the cytokines are directly responsible for the clinical manifestations or whether they are a result of the pathophysiology is unclear. In an effort to clarify the roles of cytokines in the development of OHSS, we recorded data on cytokine fluctuation in blood and ascites in a patient with OHSS during hospitalization. Treatment for OHSS is still controversial, although supportive measures such as salt and water restriction and central volume replacement are commonly accepted. Paracentesis and thoraco-
centesis of accumulated fluid are performed only when the condition is life threatening. We describe a patient with OHSS who underwent paracentesis for symptom relief. Furthermore, we show the daily fluctuations of cytokines in an attempt to monitor the correlation between the severity of the disease and the serial concentrations of the cytokines.

Case Report

This 30-year-old woman had been married for 3 years but had never become pregnant despite a normal sex life. She visited our hospital where unexplained primary infertility was diagnosed. We suggested intrauterine insemination (IUI) as her bilateral tubes were patent. Ovulation was induced with 100 mg oral clomiphene daily from days 3 to 7, and two ampoules of Pergonal (Serono SA, Geneva, Switzerland; 75 IU follicle-stimulating hormone and 75 IU luteinizing hormone) injected on days 6, 8 and 10. The IUI procedure was carried out on day 14. The patient was admitted to our hospital due to abdominal distension 6 days after IUI. Initially, conservative treatment did not improve symptoms, which included abdominal distension and dyspnea due to massive ascites and growing pleural effusion. From day 6 of hospitalization, 12 days after IUI, we inserted a continuous drainage catheter (nephrostomy pigtail 10 Fr, 30 cm catheter) into the peritoneal cavity using an aseptic procedure. The daily amount drained and the cytokine levels in serum and ascites were recorded. The patient’s symptoms improved as the amount of ascites drained daily decreased. She was discharged on day 14 of hospitalization. Subsequently, her pregnancy was unremarkable and she had a healthy 2,690 g female and a 2,155 g male infant by cesarean section at 36 weeks’ gestation.

The daily amount of ascites drained and daily serum VEGF concentrations are shown in the Figure. The serum and ascites concentrations of IL-1 and TNF-α did not appear to be relevant to the progression of OHSS. There was also no correlation between the ascites concentration of VEGF and OHSS symptoms. More data are required to formulate a possible relationship.

Discussion

In recent decades, several reports have investigated and confirmed the pathophysiologic changes associated with OHSS in serum, ascites, and pleural effusion. There is elevation of multiple cytokines, including IL-2, IL-6, and IL-8 [1,2,4,5]. VEGF is also increased [1,3]. Most studies used the expression of these cytokines in serum and ascites to predict the occurrence and severity of OHSS. One report suggested that cases of OHSS did not require hospitalization if aggressive paracentesis and thoracocentesis were carried out in the outpatient department [6]. From our results, we agree that aggressive treatment is beneficial. With conservative treatment, patients mostly suffer from abdominal distension, oliguria, and dyspnea. It is reasonable to require bed rest, home monitoring with intermittent outpatient paracentesis, and adequate albumin administration.

In this case, we attempted to monitor the daily fluctuations of a series of cytokines. IL-6 may be the most relevant to OHSS; several reports indicate that it is a possible factor in the mechanism of OHSS. Moreover, many investigations have observed a significant elevation in IL-6 in serum, ascites, and plural effusion in OHSS patients. IL-6 is produced by monocytes, endothelial cells, T cells, and fibroblasts. Its production is induced by shock-triggering cytokines such as IL-1 and TNF-α [1]. IL-6 is produced during follicular
neovascularization, and it has been reported to be involved in angiogenesis and hyperpermeability [7]. It is also produced by ovarian tumor cells and may play an important role in maintaining tumorigenicity with tumor vessel formation, and in the development of ascites associated with ovarian cancer [4,8]. A role for IL-6 in normal ovarian function has been suggested by the observation that IL-6 RNA is produced during neovascularization or angiogenesis during the development of ovarian follicles [4]. We found no correlation between our patient’s daily IL-6 levels in serum and ascites and her symptoms. This result does not support the use of IL-6 levels to predict the occurrence and severity of OHSS.

IL-8 is also a key cytokine related to angiogenesis. Recently, significant elevations of IL-8 in ascites have been observed in OHSS patients, without significant changes in serum [7]. IL-8 has also been correlated to the development of and recovery from OHSS, but the relationship was not significant. Our results suggest that it is unreasonable to believe that IL-8 would be a good predictor of the occurrence and severity of OHSS. Conclusions cannot be drawn without further prospective investigations.

VEGF is also considered a factor in the pathogenesis of capillary leakage in OHSS [9]. Ovulation induction may lead to high levels of VEGF expression due to the growth of a large number of follicles and formation of the corpora lutea, which results in vascular leakage [10]. High VEGF concentrations are known to increase vascular permeability and lead to plasma extravasation followed by pronounced hemoconcentration. An elevated VEGF concentration has been noted in the serum and ascites of OHSS cases [9]. In addition, VEGF plasma levels are positively correlated with OHSS [10]. In our case, the fluctuation of VEGF in serum was obviously relevant to the volume of ascites being drained (Figure).

References